

SUBSTANCE USE IN BIPOLAR DISORDER - ASSOCIATIONS WITH AGE AT ONSET, TREATMENT DELAY AND OUTCOME

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TOP Study

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Oslo, Norway, 2011

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*Series of dissertations submitted to the
Faculty of Social Sciences, University of Oslo
No. 249*

ISSN 1504-3991

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Cover: Inger Sandved Anfinssen.
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TABLE OF CONTENTS

Acknowledgements	5
List of papers	6
Abbreviations	7
Definitions	8
1 INTRODUCTION.....	9
1.1 General introduction	9
1.1.1 Bipolar disorder	9
1.1.2 Substance use and use disorders	9
1.1.3 The close relationship between bipolar disorder and substance abuse	10
1.2 Bipolar disorder	11
1.2.1 The diagnostic criteria	11
1.2.2 Epidemiology	11
1.2.3 Biological and neurocognitive abnormalities	12
1.2.4 Etiology	12
1.2.5 Course and implications	14
1.3 Substance use and abuse in bipolar disorder	16
1.3.1 The prevalence of substances use disorders in bipolar disorder	16
1.3.2 Excessive substance use in bipolar disorder	17
1.3.3 Hypotheses for the co-occurrence of SUD and psychiatric disorders	18
1.3.4 The effect of substance use on the outcome of bipolar disorder	19
1.4 The onset and early phases of bipolar disorder	20
1.4.1 Age at onset	20
1.4.2 Substance use as a risk factor for bipolar disorder	21
1.4.3 Early identification of bipolar disorder	23
1.4.4 The long road to adequate treatment in bipolar disorder	23
1.5 Synopsis and introduction to aims	26
2 AIMS OF THE THESIS.....	27
3 MATERIAL AND METHODS.....	28
3.1 Setting	28
3.2 Material.....	28
3.3 Methods	30
3.3.1 Diagnostic assessment	30
3.3.2 Assessment of sociodemographic characteristics, symptoms and illness course	30
3.3.3 Excessive substance use assessment and definitions	31
3.3.4 Temporal sequencing	33
3.3.5 Treatment delay	33
3.4 Statistical analyses.....	34

4	RESULTS AND SUMMARY OF PAPERS.....	35
5	DISCUSSION	38
5.1	Methodological issues	38
5.1.1	Sample representativity	38
5.1.2	Reliability and validity of assessments	40
5.2	Ethical considerations.....	41
5.3	Discussion of main results	42
5.3.1	The prevalence of lifetime illicit substance use in bipolar disorder.....	42
5.3.2	The relationship between excessive substance use and the outcome of bipolar disorder	43
5.3.3	The relationship between excessive alcohol and cannabis use and the age at onset of bipolar disorder	45
5.3.4	Excessive substance use and the onset of bipolar disorder.....	46
5.3.5	The relationship between excessive substance use and treatment delay.....	47
5.3.6	Strengths and limitations of the study	48
5.4	Theoretical implications	50
5.5	Clinical implications	51
5.6	Implications for future research.....	52
6	CONCLUSIONS	53
	Reference List	54
	Appendix	71
	Papers I, II and III	

Acknowledgements

The studies on which this thesis is based are part of the Thematically Organized Psychosis (TOP) Study, which started off in 2002. The study is funded by grants from the South Eastern Norwegian Health Authorities (Helse Sør-Øst).

Firstly, I want to thank the patients that have invested time and effort in the study assessments; for disclosing their feelings and experiences and patiently completing enduring interviews and tests. Secondly, I am deeply grateful towards my main supervisor, Senior Scientist Ingrid Melle, both for generously sharing from her massive pool of knowledge and experience, and for her continuous warm support and encouragement, especially during tough periods. I have also greatly appreciated the always to-the-point feedback from my second supervisor and leader of the TOP Study, Professor Ole Andreassen, who has great analytic skills and an ability to consider the complexity of the field in which we work. The contributions from my other second supervisor Professor Kjetil Sundet have also been invaluable thanks to his great scientific and educational skills.

Working in the TOP Study has been extremely developing and meaningful for me because of the many qualified and uniquely inspiring people that have been my colleagues. Akiha Ottesen Berg, Aina Holmén, Andreas Ringen, Carmen Simonsen, Charlotte Fredslund Hansen, Elisabeth Ann Barrett, John Engh, Kristin Lie Romm, Sara Larsson and Sofie Aminoff have all been great fun to be with on top of contributing to my work in many ways. I have also appreciated the collaboration with and presence of Anja Vaskinn, Ann Færden, Astrid Birkenæs, Christian Thoresen, Cecilie Hartberg, Tone Hellvin, Torill Ueland and Unn Haukvik. I hope the future will bring us together again for further collaboration.

Furthermore, I would like to thank the members of the "FoU forskningsmøte" for the opportunity to present my work there and receive valuable feed-back in several phases of the process, and Professor Stein Opjordsmoen for great clinical supervision.

Eivind Bakken, Eva Mjelde, Linn Kleven, Merete Øibakken and Ragnhild Storli in the TOP administration also deserve warm appreciation, as they have always made great effort to run things smoothly and take good care of the patients. Furthermore, Thomas Bjella, responsible for the IT group, has been very helpful and efficient regarding the database and technical questions. All clinicians who have been very helpful in referring patients to the study also deserve my gratitude.

Lastly, but not least, I want to thank my husband Magnus Vik Lagerberg who has continuously provided priceless support and belief in me and this project. Also, my children Rasmus and Jonatan deserve gratitude for filling my thoughts and life with so much more of value than work.

List of papers

Paper I

Lagerberg, T.V., Andreassen, O.A., Ringen, P.A., Berg, A.O., Larsson, S., Agartz, I., Sundet, K., Melle, I.
Excessive substance use in bipolar disorder is associated with impaired functioning rather than clinical characteristics, a descriptive study. BMC Psychiatry 2010, 10:9.

Paper II

Lagerberg, T.V., Sundet, K., Aminoff, S., Berg, A.O., Ringen, P.A., Andreassen, O.A., Melle, I.
Excessive cannabis use is associated with earlier age at onset compared to excessive alcohol use in bipolar disorder. Accepted with minor revisions in European Archives of Psychiatry and Clinical Neuroscience.

Paper III

Lagerberg, T.V., Larsson, S., Sundet, K., Hansen, C.F., Hellvin, T., Andreassen, O.A., Melle, I.
Treatment delay and excessive substance use in Bipolar Disorder. J of Nerv Ment Dis 2010 Sep;198(9):628-33.

Abbreviations

AAO	Age at onset of first affective episode in bipolar disorder
BAS	Behavioral Approach System
BD	Bipolar disorder
BD I	Bipolar I disorder
BD II	Bipolar II disorder
BD NOS	Bipolar disorder not otherwise specified
DSM	Diagnostic and Statistical Manual for Mental Disorders
GAF	Global Assessment of Functioning Scale - Split version
GAF-S	Global Assessment of Functioning Scale - Symptom subscale
GAF-F	Global Assessment of Functioning Scale - Functioning subscale
IDS-C	Inventory of Depressive Symptomatology - Clinician rated
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
SCID-I	Structured Clinical Interview for DSM-IV Axis I disorders
SUD	Substance use disorder
TOP	Thematically Organized Psychosis Study
YMRS	Young Mania Rating Scale

Definitions

Drugs/Illicit substances: Drugs that are illegal to use or deposit in Norway.

Euthymic: A normal mood state, neither depressive nor elevated.

Excessive substance use: DSM-IV substance use disorder or predominantly daily use of alcohol and/or predominantly weekly use of drugs (other than alcohol) during a period of at least 4 years.

Sequencing of onsets: The temporal relationship between the onset of BD and the (possible) onset of excessive substance use:

Primary BD: When there has been no excessive substance use prior to the onset of BD.

Secondary BD: When excessive substance use precedes the onset of the BD.

Substance use disorder: DSM-IV substance abuse or dependence

Substances: Drugs and alcohol

The outcome of BD: Clinical and functional characteristics related to both illness course and current status.

1 INTRODUCTION

1.1 *General introduction*

1.1.1 **Bipolar disorder**

Bipolar disorder (BD) is a severe mental illness causing significant individual suffering and functional loss. It is characterized by severe mood swings; periods with distinctly depressed and elevated mood in between periods with normal mood (euthymia). Melancholy (i.e. depression) and mania were first described by the ancient Greeks and are thus among the oldest reported of human illnesses. While Hippocrates (460-337 BC) was the first to systematically describe mania and melancholia, the first known writings of these two phenomena as part of the same disease dates back to the 1st century AD. Around 1850, BD was for the first time formulated as a separate entity of mental disorder by Jean-Pierre Falret: “la folie circulaire” (Angst & Marneros, 2001). The concept of “manic-depressive insanity” was developed by Kraepelin towards the end of the 19th century and included both recurrent depression (without mania), manic, hypomanic and mixed episodes (Kraepelin, 1899).

It was not until the midst of the 20th century that a distinction between recurrent depressions only (unipolar disorder) and recurrent manias with depressions (bipolar disorder) was made. This distinction was incorporated in the international diagnostic system Diagnostic and Statistical Manual of Mental Disorders (DSM)-III (American Psychiatric Association, 1980), and has persisted since then. In 1976, Dunner and co-workers distinguished BD I from BD II on the basis of differences in course and family history of affective symptomatology (Dunner et al., 1976), although the latter has been questioned by later studies (Edvardsen et al., 2008). Today, in the fourth edition of the DSM (DSM-IV), BD comprises BD I, BD II, cyclothymia and BD NOS (Not Otherwise Specified) (American Psychiatric Association, 1994). The other diagnostic system, the International Classification of Diseases, has similar diagnostic criteria for BD (World Health Organization, 2004). There are, however, minor differences such as the requirement of more than one affective episode in the ICD-10 as opposed to the DSM-IV, where one manic episode is sufficient to fulfill BD I criteria. In this thesis, the DSM-IV is used.

1.1.2 **Substance use and use disorders**

The use of psychoactive substances, i.e. substances that act on the central nervous system and alters brain functioning may have been part of human behavior and culture since the emergence of our species (Durrant & Thakker, 2003). Alcohol and drugs are used in most countries of the world

today, but the extent and patterns of use vary between countries and cultures and over time. Alcohol and drug use are estimated to be responsible for approximately 5% of the global burden of disease (Rehm et al., 2006). Since the 1980's, there has been a substantial increase in the production and use of illicit drugs throughout the world, with important consequences for public health (World Health Organization, 2000). In a prevalence study of seven international sites (Europe, North- and Latin America), the percentage of the population that reported lifetime use of alcohol was in the range of 43-86%, the lifetime use of cannabis five or more times ranged from 2-30%, and the lifetime use of other drugs ranged from 2-19% (Vega et al., 2002).

Substance use may progress from use to addiction, which is usually defined as a persistent, compulsive and uncontrolled dependence of a substance. Research has made considerable progress the last decades in gaining knowledge on the psychobiological mechanisms by which substance use is reinforced and addiction develops (Koob & Le Moal, 2001). Substance use disorders (SUD) were included as mental disorders in the DSM since the first edition (American Psychiatric Association, 1952). In the DSM-IV, substance use is considered as a disorder when it implies a "maladaptive pattern of substance use which leads to substantial clinical discomfort or functional loss". The diagnostic system subdivides SUDs into two disorders with increasing severity: *substance abuse* and *substance dependence*, characterized by two different sets of symptom criteria. *Abuse* is defined by negative consequences of social, forensic or risk behavioral character. *Dependence* is defined by two major characteristics: a compulsion to take the drug with a narrowing of the behavioral repertoire toward excessive drug intake, and a loss of control in limiting intake. The most severe type of dependence, often referred to as addiction, is signified by a physiological dependence involving tolerance and withdrawal symptoms. This is more likely for some drugs (alcohol, cocaine and opioids) than for others (hallucinogens). According to the DSM-IV, the symptoms of abuse or dependence must have been present within the same year in order to fulfill diagnostic criteria. Enduring excessive use is necessary in order to develop dependence. Regarding abuse, the substance related problems must have occurred repeatedly or been persistent (American Psychiatric Association, 1994).

1.1.3 The close relationship between bipolar disorder and substance abuse

More than a century ago, a high co-occurrence of alcohol abuse among patients with BD was noted by Kraepelin (Goodwin et al., 2007). Since then clinical and epidemiological studies across different populations have confirmed this observation (Cassidy et al., 2001; Grant et al., 2005; Regier et al., 1990). In fact, the rates of SUD appear to be higher in BD than in most other psychiatric disorders. The mechanisms behind this common co-occurrence are largely unknown, and although substantial

effort to gain knowledge on important aspects of this relationship has been made in research the last decades, several issues remain unclear. The current study aims at clarifying some of these issues.

1.2 *Bipolar disorder*

1.2.1 The diagnostic criteria

Diagnostic systems for mental disorders are descriptive, implying that it is based on the patient's experiences, thoughts and behavior. The DSM-IV criteria were established in 1994 by an expert committee, and extensive work has been conducted to ensure the diagnoses' validity and reliability. The diagnostic systems of today are categorical, in the sense that a diagnosis is given only if sufficient criteria for the disorder are met, and polythetic, i.e. patients within a category have some, but not necessarily all characteristics in common.

BD comprises depressive, hypomanic, manic and/or mixed episodes (diagnostic criteria for the episode subtypes are presented in Table 1 in the Appendix). A BD I diagnosis may be given on the basis of manic episodes only, while in BD II, at least one hypomanic episode and one major depressive episode are required to fulfill diagnostic criteria. The diagnosis of BD NOS refers to bipolar symptoms that do not fulfill criteria for a specific BD (i.e. episodes of shorter length or cases in which it cannot be determined whether the BD is primary or secondary to a somatic state or substance use) (American Psychiatric Association, 1994). During the recent years, attempts have been made to differentiate between several additional BD subtypes. However, the main focus now seems to be on a natural continuum from transient to persistent manic manifestations of varied length, severity and frequency (Angst & Marneros, 2001). During the recent years, there has also been a movement towards a more dimensional diagnostic system for severe mental disorders, based on the increasing empirical evidence for considerable overlap in both the clinical, genetic, neuropathological and neurocognitive features of bipolar disorder and schizophrenia (Craddock & Owen, 2007; Murray et al., 2004). This view is also supported by previous findings from our research group (Simonsen et al., 2009).

1.2.2 Epidemiology

The lifetime prevalence of BD is generally stated to be 1% for BD I and 1-2% for BD II, with somewhat more uncertain rates for BD II due to difficulties distinguishing hypomania from normal mood-fluctuations in community samples (Goodwin et al., 2007; Kessler et al., 2007). The prevalence of BD is believed to be relatively consistent across cultures and regions, however,

prevalence rates vary from 0.1 - 1.8% for bipolar I disorder and 0.3 - 3.0% for bipolar II disorder across studies (Angst, 1998; Sherazi et al., 2006; Weissman et al., 1996). It is not known whether this variation is caused by differences in methodology or by actual variation across populations.

1.2.3 Biological and neurocognitive abnormalities

Our understanding of the pathophysiology of BD remains limited. However, several neurobiological abnormalities have been identified that are likely to be underlying features of the disorder, such as immunological, neuroendocrinological, and molecular biological deviations (Langan & McDonald, 2009). Furthermore, neuroimaging and post mortem studies have identified both structural and functional disturbances in brain areas involved in the regulation of emotions and motivated behavior as well as cognition, such as regions in the prefrontal and orbitofrontal cortex, and the amygdala and ventral striatum (Phillips et al., 2008). Structural abnormalities of the CNS appear to be more pronounced in BD I than BD II; in a recent study from the TOP study group, only BD I patients showed cortical thinning in several brain regions, while BD I and II combined showed several substantial subcortical volume reductions relative to healthy controls (Rimol et al., 2010). BD patients, even during euthymic periods, also show neurocognitive impairment in a number of domains, the largest seen in aspects of executive function and verbal memory (Robinson et al., 2006). The severity of neurocognitive deficits is positively correlated with illness duration and number of previous manic episodes (Martinez-Aran et al., 2004). Furthermore, in a previous study from our group patients with BD I were shown to be more severely affected neurocognitively than patients with BD II (Simonsen et al., 2008), although the severity of impairments was more strongly related to the presence of lifetime psychotic symptoms than to the bipolar diagnostic subtype (Simonsen et al., 2009). Neurobiological and neuropsychological phenomena are beyond the scope of this thesis, and will thus not be discussed in further detail.

1.2.4 Etiology

The etiology of BD is still to a large extent unknown, but family- and twin-studies have provided strong evidence that vulnerability to the disorder is genetically transferred (Smoller & Finn, 2003), with heritability estimates around 0.8 (Kendler et al., 1995). Multiple genes or complex genetic mechanisms appear to be involved. Recent genome-wide association studies have identified some gene variations that influence susceptibility to BD, although effect sizes are small (Craddock et al., 2009; Djurovic et al., 2010).

Since the monozygotic twin concordance rate is far below 100% (38.5 - 62%) (Smoller & Finn, 2003), environmental factors must influence the phenotype. Even though research so far is

limited, there is evidence that childhood trauma (Garino et al., 2005), stressful life events (Horesh & Iancu, 2010), cannabis use (van Laar et al., 2007) and migration (Swinnen & Selten, 2007) are associated with heightened risk for BD. Virus infections and obstetric complications have also been suggested as potential environmental risk factors, although current evidence seems weak (Scott et al., 2006; Yolken & Torrey, 1995). Thus, BD appears to develop from an interaction between genetic, neurobiological and environmental factors.

The stress-vulnerability model

The notion that environmental factors are risk factors for BD is in part based on stress-vulnerability models. Such models have been postulated for psychiatric disorders in general and more specifically for affective and psychotic disorders (Harris & Brown, 1989; Nuechterlein & Dawson, 1984; Post et al., 1986; van Winkel et al., 2008). Stress-vulnerability models generally suppose that psychiatric symptoms emerge whenever a threshold of stressors exceeds an individual's vulnerability level, conceptualized as a stable within-person characteristic (van Winkel et al., 2008). The notion of vulnerability is however complex and difficult to define and measure, and includes features such as family history, different biological factors, personality or behavioral attributes and experiences of damaging circumstances in the past. The most commonly used vulnerability marker for BD is a family history of affective disorder among close relatives. However, an experienced stressor may also increase an individual's vulnerability in that it subsequently enhances the individual's stress sensitivity. This notion is conceptualized in the behavioral sensitization model for BD (Post, 1992).

The kindling and behavioral sensitization models for bipolar disorder

Life events seem to play a role not only in the onset of the first affective episode, but also in relapses (Hammen & Gitlin, 1997; Kennedy et al., 1983). However, early clinical observations have indicated that the role of environmental stressors is greater for initial than later episodes of mania and depression (Kraepelin, 1921). This phenomenon has formed the basis for electrophysiological kindling (progressive vulnerability to seizures) and behavioral sensitization (progressive change in psychomotor stimulant response) as analogous models for the course of affective disorders (Post et al., 1986). The kindling model suggests that stressful events trigger the first affective episodes while later episodes may eventually become independent from external events. Behavioral sensitization provides a model for the development of the increasingly severe and rapid recurrences seen in a subgroup of patients in response to repeated stress of equal or reduced magnitude (Post et al., 1986; Post, 1992). Furthermore, there are also indications of cross-

sensitization, in that one type of stimulus (e.g. psychosocial stress) increases the sensitivity for other types of stimuli (e.g. substance use) (Swann, 2010). Several phenomena appear to support these models: the fact that affective disorder is recurrent for the majority of patients, the tendency for reduced cycle length (time between episodes) with increasing number of prior episodes in some patients (Kessing & Andersen, 2005), and the greater prevalence or severity of life events preceding the first affective episode compared to later episodes (Ambelas, 1987). However, later identification of methodological flaws in some of the studies as well as inconsistencies in recent findings (Dienes et al., 2006; Hlastala et al., 2000; Johnson et al., 2000), leave unresolved questions regarding the validity of these models.

1.2.5 Course and implications

Illness course and comorbidity

Bipolar disorder usually has its onset in the early twenties to the early thirties (Goodwin et al., 2007). It is a highly recurrent and chronic disorder. Even though substantial improvement in remission and relapse rates is achieved with mood-stabilizing medication such as lithium, antipsychotic and anti-epileptic agents, approximately 75% of patients relapse within five years when followed along in naturalistic treatment settings (Gitlin et al., 1995). The ratio of time spent with depressive relative to manic symptoms appears to be 3:1, and patients experience affective symptoms approximately half of the time (Judd et al., 2002). Patients also appear to spend more time with subsyndromal affective symptoms than in episodes (Joffe et al., 2004). However, only a subgroup of patients seem to develop progressive cycle-acceleration over the course of illness (Salvatore et al., 2007). As the acute manic episodes are more severe in BD I compared to hypomania in BD II, BD I is considered to be a more severe illness. However, the overall disease burden may be similar for the two bipolar subtypes, since BD II appears to have a more chronic and predominantly depressive course compared to BD I (Judd et al., 2003).

Comorbid medical disorders and -risk factors with increased mortality rates and shorter life span is also common in BD (Birkenaes et al., 2007; McIntyre et al., 2007). Furthermore, in addition to high rates of substance use disorders (McElroy et al., 2001), several comorbid psychiatric disorders such as personality disorders and anxiety disorders are frequent (Fan & Hassell, 2008; Grant et al., 2005).

Suicidal behavior

From 10% to 56% of individuals with BD attempt suicide at least once during their lives (Goodwin et al., 2007). The total risk for death by suicide in BD has been estimated to approximately 20%,

which is more than 20-fold higher than in the general population (Tondo et al., 2003) and accounts for a considerable proportion of the excess mortality in BD. Suicidal behavior is more frequent early in the illness course (Ösby et al., 2001; Tondo et al., 2007) and in association with depressive episodes (Isometsä et al., 1994). Rates appear to be similar for BD I and II (Novick et al., 2010), however, there is evidence that suicide acts are more lethal in BD II compared to BD I (Tondo et al., 2007).

Functional loss in bipolar disorder

Bipolar disorder is among the 10 leading causes of disability-adjusted life years (years of life lost to premature death and years lived with disability) among 15-44 year olds in the world (World Health Organization, 2001). BD implies compromised functioning in several domains even with sustained recovery. One study showed that while 98% of the patients attained syndromal recovery 2 years after the first episode, only 31% reached functional recovery (defined as return to baseline vocational status and living situation) (Tohen et al., 2000). Reduced functioning in BD is also seen in marriage rates (Mitchell et al., 2009) and in social and leisure activities (Blairy et al., 2004). Several studies have also shown that individuals with BD have reduced quality of life compared to healthy controls (Michalak et al., 2005). In a recent study from the TOP study group, BD patients rated themselves on the same level of social functioning as did the schizophrenia patients, both groups significantly lower than healthy controls (Simonsen et al., 2010). BD I and II also appear to have a similar level of impairment in psychosocial functioning (Ruggero et al., 2007). Functional impairment is primarily associated with clinical characteristics (comorbidity, symptom severity etc.) but also with neurocognition (Sanchez-Moreno et al., 2009), also supported by previous findings from our study group (Simonsen et al., 2010). Despite all indications of impaired functioning, there is biographical evidence that BD is associated with creativity and scholastic achievement (Jamison, 1995). The scientific evidence for such an association has been weak, but a higher educational level among BD patients compared to the general population has been found (Mitchell et al., 2009), and in a recent prospective epidemiologic study excellent school performance was associated with a fourfold increase in the risk for later BD (MacCabe et al., 2010). How these findings converge with the neurocognitive impairment associated with BD is largely unknown, but may be related to a deteriorating effect of recurrent affective episodes on cognition (Ferrier & Thompson, 2002).

Treatment of bipolar disorder

Until the therapeutic benefits of lithium were discovered in the midst of the 20th century, there was no efficacious treatment for BD. Later, anticonvulsants and antipsychotic agents have also proved

effective, and along with lithium these medications are recommended treatments of BD according to today's expert consensus guidelines (Grunze et al., 2004). However, pharmacological treatments are still suboptimal, especially regarding functional impairment, which has led to the development and adjustment of several psychotherapeutic interventions for BD, such as psychoeducation, Interpersonal and Social Rhythm Therapy, cognitive behavioral therapy and family therapy. These have all shown promising results in reducing recurrence rates, hospitalizations and functional impairment (Colom et al., 2003; Miklowitz & Scott, 2009).

1.3 Substance use and abuse in bipolar disorder

1.3.1 The prevalence of substances use disorders in bipolar disorder

Substance use seems to be a particular problem in BD, recognized in both epidemiological and clinical studies. The Epidemiological Catchment Area study conducted in the USA in the 1980's reported higher prevalences of SUDs in BD than in other Axis I disorders (including schizophrenia, anxiety disorders and other affective disorders), with a lifetime prevalence of 46% for alcohol use disorders and 41% for drug use disorders (Regier et al., 1990). In the more recent NESARC study, the reported prevalences were 58% and 38% respectively (Grant et al., 2005). With the starting point in the SUDs, another epidemiological study reported that the lifetime risk for mania was increased with an odds ratio of 9.7 in persons with alcohol dependence and 8.4 in drug dependence (Kessler et al., 1996). Alcohol use disorders are more prevalent in men than in women, but when compared to prevalence rates in the general population, the risk for developing alcohol use disorders in BD is considerably greater for women than for men (Frye et al., 2003).

In clinical studies of BD I samples reporting the prevalence for all major substance use disorders separately, the lifetime rates range from 36 to 49% for alcohol, 17 to 36% for cannabis, 4 to 22% for stimulants (cocaine and amphetamines), 3 to 9% for opiates, 3 to 7% for sedatives and 4 to 7% for hallucinogens (Cassidy et al., 2001; Goldberg et al., 1999; McElroy et al., 2001; Pini et al., 1999; Winokur et al., 1998). These rates clearly exceed that of the general population. The prevalence of different SUDs in BD II disorder is less investigated. To the best of my knowledge, only two studies have investigated rates for all major lifetime substance use disorders in BD II, and these report the following rates: 22 and 39% for alcohol, 10 and 6% for cannabis, 6 and 6% for stimulants, 4 and 6% for cocaine, 0 and 0% for opiates, 2 and 6% for sedatives and 2 and 6% for hallucinogens (Chengappa et al., 2000; McElroy et al., 2001). Thus, the rates appear to be somewhat lower in BD II compared to BD I, but the differences are not prominent.

Possible reasons for differences in SUD prevalence

The prevalence rates of SUD in BD vary widely across different geographical settings, from 49% with alcohol- and 44% with drug use disorders in a study from the US (Cassidy et al., 2001), through 28% with alcoholism and 14% with drug addiction in a study from Brazil (Neves et al., 2009) to 10% with alcohol use disorders and none with drug use disorders in a study from Taiwan (Tsai et al., 1997). Such variations could be reflecting differences in substance use in the general populations from which the BD samples are recruited, but could also be related to different methodologies used in these studies. To my knowledge, there has been only one multinational study of substance misuse in BD where a common methodology was used across sites, reporting higher prevalence rates in the US than in Europe (Germany/Netherlands) (47% vs. 27%) (Post et al., 2008). Still, most studies investigating the prevalence of SUD in BD are conducted in the US where the rates of illicit drug use in the general population are relatively high compared to other countries (Vega et al., 2002). Thus, there is a need for prevalence studies conducted in other countries than the US, preferably comparing the substance use of BD subjects with that of a reference population from the same geographical area and within the same time period. In the current study, the prevalence of lifetime use of illicit substances in a sample of BD patients is compared to that of the general population.

1.3.2 Excessive substance use in bipolar disorder

Most studies of the consequences of substance use in BD have only investigated substance use that meets diagnostic SUD criteria. Investigating a broader range of substance use could be relevant because people with severe mental disorders appear to be more sensitive to and more likely to experience negative consequences also from using relatively small amounts of psychoactive substances, compared to healthy individuals (Bizzarri et al., 2007; Mueser et al., 1998). For instance, euthymic individuals with BD had increased behavioral response to intravenous amphetamine compared to healthy controls in an experimental study (Anand et al., 2000). In BD, moderate alcohol consumption has been shown to be associated with more severe manic symptoms compared to abstinence, and to poorer social and familial adjustment and increased health-care use (Goldstein et al., 2008). Thus, in patients with severe mental illness, negative consequences from substance use may occur long before symptoms of abuse or dependence have developed. There has recently been increasing focus on including also substance use not fulfilling SUD criteria when investigating the impact of substance use on illness onset and clinical outcomes

in severe mental disorders (Goldstein et al., 2008; Henquet et al., 2006; Ringen et al., 2008; Ringen et al., 2009). However, little is still known regarding what level of use – i.e. amount and/or frequency - should be considered as excessive use in BD.

Investigating substance use in BD patients without SUD may also increase our understanding of the psychopathology underlying the increased risk of abuse or dependence. Whether the propensity to substance use is part of the BD itself or something that characterizes only a subgroup is still unclear. To the best of my knowledge, only one study has assessed excessive substance use in BD, reporting that 46% had SUDs, and 8% had SUD-subthreshold substance use. In addition, the authors indicated that another substantial proportion used illicit substances occasionally (Sbrana et al., 2005). We thus need more knowledge on the prevalence of SUD-subthreshold substance use in BD. The present study aims to assess the prevalence of substantial substance use that falls below the cut-off of DSM-IV diagnostic criteria. In this thesis, *excessive use* is defined not only by the existing SUD criteria (i.e. criteria including consequences of use), but also by criteria based on frequency and duration of use. We also investigate differences and similarities in characteristics of both substance use and clinical characteristics between patients with SUD, patients with SUD-subthreshold substance use and patients with neither, to explore if also substance use below the SUD threshold appears to be harmful for patients with BD.

1.3.3 Hypotheses for the co-occurrence of SUD and psychiatric disorders

Comorbidity with SUDs is also common in other psychiatric disorders. The highest prevalence of SUDs is found in personality disorders such as antisocial and borderline personality disorders (Sher & Trull, 2002), but it is also high in other symptom disorders such as schizophrenia (Swartz et al., 2006), major depressive disorder and anxiety disorders (Kessler et al., 1997). Thus, a close relationship appears to exist between SUDs and psychiatric disorders in general. Research also indicates that many of the individual factors that influence the susceptibility to develop SUDs, for instance genetics (Goldman et al., 2005), personality traits (such as novelty-seeking) (Fergusson et al., 2008), stress (Campbell et al., 2009; Sinha, 2008) and coping skills (Anderson et al., 2006) are linked to a general vulnerability for psychopathology.

There are several hypotheses on the association between severe mental illness (including BD) and SUDs, and these can be organized into four general models: 1) common factor models, 2) secondary SUD models, 3) secondary psychiatric disorder models, and 4) bidirectional models (Mueser et al., 1998). Briefly, the common factor models hypothesize that risk factors are shared between the two disorders (e.g. genes, personality traits). The secondary SUD models suggest that severe mental illness increases the risk of developing SUDs (e.g. as an attempt to self-medicate

psychiatric symptoms). Secondary psychiatric disorder models propose that SUDs may trigger severe mental illness in individuals that would not otherwise have developed the disorder, and bidirectional models hypothesize that either disorder increases the vulnerability for the other disorder through ongoing interactional effects (Mueser et al., 1998). All models have gained some support from research on SUD and BD comorbidity, and they are not mutually exclusive but may account for parts of the comorbidity within groups and individuals.

1.3.4 The effect of substance use on the outcome of bipolar disorder

As substance use is known to alter affective states, and substance dependence to cause long-lasting changes in brain regulatory mechanisms (Koob & Le Moal, 2001), substance use may be expected to act negatively upon the symptoms and course of BD. Accordingly, there is growing evidence that SUDs have a negative impact on aspects of the BD. However, the research literature tends to report this impact as broad and global, instead of being specific regarding which areas where excessive substance use seems to have an impact. Areas of interest here are both affective symptoms, illness course (number of episodes, hospital admissions etc.), and functional status including occupational status and global functioning. There is relatively consistent evidence that BD patients with SUD have slower recovery and faster relapses (Keller et al., 1986; Tohen et al., 1990), as well as elevated rates of suicidality (Cardoso et al., 2008) and medication non-adherence (Bauer et al., 2005) compared to patients without SUD. Other relatively consistent findings are that BD patients with SUD do *not* have an increased prevalence of psychotic symptoms (Verduin et al., 2005) nor an increased number of affective episodes (Nolen et al., 2004) compared to BD without SUD. Findings are however more diverging regarding the rates of rapid cycling (Haro et al., 2006; MacKinnon et al., 2003), mixed episodes (Goldstein et al., 2008; Himmelhoch et al., 1976), the severity of affective symptoms (Salloum et al., 2002; Sonne et al., 1994) and the number or length of hospital admissions (Pini et al., 1999; Singh et al., 2005), where some studies find that these are increased in BD with SUD compared to BD without, and some find that they are not. Regarding functional variables such as global functioning (O'Connell et al., 1991; Winokur et al., 1995), social functioning (Kusznir et al., 2000; Tsai et al., 1997), educational level (Cardoso et al., 2008; Verduin et al., 2005) and quality of life (Cardoso et al., 2008; Mazza et al., 2009), the findings are also diverging.

In addition to the conflicting findings, there are also methodological inconsistencies across the studies. Furthermore, effect sizes that may inform about the probable clinical impact are rarely reported. Thus, a critical review of the literature indicates that SUDs are probably not as consistently and globally associated with a more severe course and outcome as frequently

indicated in the literature, and further research is needed to clarify these issues. In the current study, we study potential differences in a wide range of clinical and functional characteristics between patients with and without excessive substance use.

1.4 The onset and early phases of bipolar disorder

There has been a growing focus on factors associated with the age- and mode of onset of BD. This increase in interest has several reasons including the growing general focus on early intervention strategies in severe mental illness, the possible increase in the prevalence of child- and adolescent BD as well as intensified efforts to identify risk factors for BD. One of the strongest predictors of a more severe illness course in BD, including increased psychiatric comorbidity, is an early onset (Schurhoff et al., 2000). Unraveling the factors associated with early onsets may be a path towards better understanding of disease mechanisms and prevention of severe outcomes. The present study will investigate factors associated with age at onset (AAO) in BD.

1.4.1 Age at onset

Several factors have been shown to be related to AAO in BD. Recent studies have found differences in AAO between research sites: Higher rates of childhood- or adolescent onset are more often reported from US studies (around 60%) than from European studies (around 30%) (Baldessarini et al., 2010; Post et al., 2008) including findings from our own study group (Larsson et al., 2010), even though there are exceptions (Baldessarini et al., 2010; Morken et al., 2009; Oedegaard et al., 2009). This variation in AAO has been attributed to factors ranging from differences in genetic loading to recruitment biases or methodological discrepancies such as the definition of illness onset (Larsson et al., 2010; Oedegaard et al., 2009; Post et al., 2008).

There is extensive evidence that a family history of affective disorder is associated with earlier onsets (Leboyer et al., 2005; Rice et al., 1987; Strober, 1992). Most studies find a similar AAO for men and women (Hendrick et al., 2000), while some report earlier onsets in females (Lin et al., 2006; Suominen et al., 2009) and others earlier onsets in men with BD I (Baldessarini et al., 2010). The subtypes of BD (BD I and II) appear to have a similar AAO (Judd et al., 2003); however, earlier onset in BD I was recently reported (Baldessarini et al., 2010), while a previous report from our study groups indicates that patients with BD II have the earliest onsets (Larsson et al., 2010).

An early onset has also been associated with increased risk for substance use disorders, especially of illicit substances (Carlson et al., 2000; Carter et al., 2003; Ernst & Goldberg, 2004; Goldstein & Levitt, 2006; Lin et al., 2006; Perlis et al., 2004), and it has been hypothesized that early onset and drug abuse may share a common genetic basis (Lin et al., 2006).

1.4.2 Substance use as a risk factor for bipolar disorder

There is growing evidence that several environmental factors may constitute risk factors for BD. One such candidate is childhood adversity, due to its high prevalence in BD and its association with both earlier onsets and more severe clinical expressions of the disorder (Etain et al., 2008; Garino et al., 2005; Leverich et al., 2002). In a study comparing several different types of childhood trauma, the earliest onset was found in patients that had experienced sexual adversity (Dienes et al., 2006). Furthermore, research has shown that life events such as loss-related events (death of spouse) or major life changes (moving, changing job) are over-represented in the period preceding the first affective episode in BD patients when compared to controls (Ambelas, 1987; Horesh & Iancu, 2010). One study also showed that BD patients without a family history of affective disorder had more life events prior to illness onset compared to those with a family history (Johnson et al., 2000), supporting the general observation that persons with low genetic vulnerability do not develop symptoms unless exposed to more severe environmental stressors. Correspondingly, in the case of equal levels of genetic vulnerability, individuals experiencing more environmental stressors would have an earlier onset of illness and than individuals without. Furthermore, in individuals with low vulnerability, environmental triggers of sufficient severity may not elicit the disorder until at a later age and/or with a milder symptom expression than in persons with a high vulnerability. In support of this hypothesis, patients with life events preceding the onset of BD appear to have a later onset than in those without precipitating stressors (Johnson et al., 2000).

The latter finding is parallel to findings on BD and substance use disorders, which is considered as another possible risk factor. This line of research has investigated if there are differences in AAO depending on whether BD precedes or follows the SUD. A later onset has been found among patients with SUD preceding the BD (DelBello et al., 1999; Falk et al., 2008; Feinman & Dunner, 1996; Fossey et al., 2006; Strakowski et al., 1996; Strakowski et al., 2005; Strakowski et al., 2007). There is also evidence for a less severe clinical course (Goldstein & Levitt, 2006; Pacchiarotti et al., 2007; Strakowski et al., 2005; Winokur et al., 1995) and lower rates of family history of affective illness (DelBello et al., 1999) in BD that appears later than (secondary to) the SUD. Taken together, these findings have been interpreted as indications that substance abuse could precipitate the manifestation of BD in these individuals (DelBello et al., 1999; Strakowski et al., 2005; Winokur et al., 1995). This effect has been proposed for both alcohol (Winokur et al., 1995), cannabis (Strakowski et al., 2007) and for any substance of abuse (Pacchiarotti et al., 2007).

Alcohol and cannabis as risk factors for BD

Other indications that SUD is a potential risk factor for BD are the psychoactive substances' tendency to mimic affective symptoms and/or interfere with neurobiological mechanisms also involved in the BD itself (Post et al., 1995). However, the pharmacological effects of substances of abuse are different. In line with this, alcohol and cannabis appear to have different effects on the course of an established BD. In a prospective study, cannabis use coincided with or preceded hypomanic or manic symptoms, while alcohol use coincided with or preceded depressive symptoms (Baethge et al., 2008). Mirroring the general population, the most commonly used substances in BD are alcohol and cannabis (Cassidy et al., 2001; McElroy et al., 2001). In another study from the TOP study group, with a sample partially overlapping the sample included in this thesis, the rates of alcohol use were found to be higher and the use of cannabis as the only drug more common in BD than in schizophrenia (Ringen et al., 2008), indicating that these substances may be of special relevance for BD. However, most clinical studies on BD have focused on either alcohol abuse alone or substance abuse in general. The present study aims to compare characteristics of patients using alcohol and patients using cannabis.

During the recent years, indications have been growing from epidemiological studies that cannabis use is a risk factor for manic symptomatology. A prospective study found that cannabis use at baseline increased the risk for onset of manic symptoms (independently from psychotic symptoms) during a 3-year follow-up period with an OR of 2.7 (Henquet et al., 2006). Another study showed that cannabis use at baseline was associated with a fivefold increase in the risk of developing BD during a 3-year follow-up, with indications of a dose-response relationship (van Laar et al., 2007). Furthermore, in a recent cohort community study of adolescents, lifetime cannabis use (more than five times) increased the risk for onset of manic symptoms with an OR of 4.3 during an 8-year follow-up period (Tijssen et al., 2010). Thus, cannabis seems to be associated with an increased risk for developing both manic symptoms and the BD syndrome.

Whether excessive alcohol use has a similar effect is less investigated. One epidemiological study investigated the sequencing of onsets of alcohol use disorders and mood disorders, and found that the alcohol use disorder preceded (hypo)mania in about half of the cases, and that the lag time until the onset of (hypo)mania was long (7.6 - 12.5 years). The authors described the possible relationship between alcohol use disorders and (hypo)mania as "temporally distal" (Falk et al., 2008). To my knowledge, no studies have investigated whether excessive use of cannabis and excessive use of alcohol are differently associated with AAO. Only one study has investigated the sequence of the onsets of cannabis abuse and BD and its relationship to AAO, showing that patients with a primary cannabis use disorder had a later onset compared to patients with no

cannabis use disorder or a secondary cannabis use disorder (Strakowski et al., 2007). This has not been replicated, and there is a need for further studies that simultaneously evaluate the associations between AAO and excessive alcohol or cannabis use.

1.4.3 Early identification of bipolar disorder

In the psychosis research field, evidence has accumulated over the last two decades indicating that early identification of psychotic symptoms is both possible and beneficial. Interventions on a population based level can reduce time from illness onset to help-seeking behavior and treatment, and this shortening of the duration of untreated psychosis appear to reduce the risk of a poor outcome (Melle et al., 2004). Considerable effort has also been made to identify and operationalize a “psychosis risk syndrome”. Successful although controversial attempts at treating such states to prevent or delay illness onset have been made (Correll et al., 2010). There has been much less focus on the early phases of BD, and this research field is thus behind the general psychosis research field regarding early identification and intervention. However, there is evidence that the risk of recurrence increases as a function of number of previous episodes in BD (Kessing & Andersen, 2005), as well as a growing documentation of substantial delays from the onset of affective episodes to the correct diagnosis (Berk et al., 2007). These issues have led to a call to extend the focus on early detection into the field of BD (Conus & McGorry, 2002; Salvatore et al., 2008). Thus, recently attempts have been made at identifying prodromal symptoms of BD (Conus et al., 2008; Conus et al., 2010; Correll et al., 2007) and risk factors for transition from subthreshold affective symptoms to a full-blown BD (Tijssen et al., 2010). However, there is a great need for more basic knowledge concerning illness identification and treatment initiation in BD.

1.4.4 The long road to adequate treatment in bipolar disorder

A substantial proportion of persons with BD do not receive psychiatric treatment (Hirschfeld et al., 2003; ten Have et al., 2002). Another problem is that many seem to experience delays from illness onset to correct diagnosis and/or initiation of adequate pharmacological treatment. In a study on patients with schizoaffective disorder or BD, median age at the first manic episode was 24 years, while the correct diagnosis was received at 30 years (Berk et al., 2007). In another study of BD patients, 44% had not received the correct diagnosis by the end of the first treatment period (Kessing, 2005), and in yet another study 34% experienced a delay of more than 10 years from first professional contact to correct diagnosis (Lish et al., 1994). Several studies have reported delays from first affective symptoms to start of adequate pharmacological treatment of approximately 9-10 years (Altamura et al., 2009; Baethge et al., 2003; Leverich et al., 2002). However, identifying BD

and initiating adequate pharmacological treatment is only possible after the first (hypo)manic episode. Little is known regarding delay defined as the time from first (hypo)manic episode to the start of adequate pharmacological treatment, and what the risk factors for such delays are. The present study aims at investigating these and other aspects of treatment delay in BD.

The consequences of long treatment delays

While long durations of untreated illness is found to be clearly associated with a more severe course and outcome in schizophrenia (Marshall et al., 2005; Melle et al., 2008), it is more disputed whether treatment delays lead to a poorer outcome in BD. Some findings indicate that the response to treatment is not associated with long treatment delays (Baethge et al., 2003; Baldessarini et al., 2007). However, long durations of untreated illness was recently shown to be linked to elevated rates of suicidality, comorbid anxiety and substance use disorders in BD (Altamura et al., 2009), possibly due to the distress caused by untreated mood symptoms.

What characterizes patients with long treatment delays?

Increased knowledge about factors associated with long treatment delays can be used to form strategies for reducing such delays. Some patient characteristics that increase the risk for treatment delays have been identified. Female patients (Baldessarini et al., 2007; Kessing, 2005; Mantere et al., 2008), patients with early onset of the BD (Altamura et al., 2009; Baldessarini et al., 2007; Berk et al., 2007; Goldberg & Ernst, 2002; Kessing, 2005; Larsson et al., 2009; Suominen et al., 2007) and patients with BD II rather than BD I disorder (Baldessarini et al., 2007; Mantere et al., 2008) appear to have longer delays.

Whether substance use increases the risk for treatment delay is not known. If substance use starts before the first BD episode, this may delay both diagnosis and onset of adequate treatment. The symptoms of substance intoxication, withdrawal and long term use may cause secondary affective symptoms that are indistinguishable from primary affective syndromes (Kleber et al., 2006) and thus delay the identification of BD (Albanese et al., 2006). After BD diagnosis, pharmacological treatment may be suboptimal, due to concern for interaction between substances and mood stabilizing agents (Albanese & Pies, 2004) and indications of poorer medication response (Tohen et al., 1998). There are few randomized controlled trials in patients with comorbid BD and SUD to guide the treatment choices. In line with this, a trend was found in one study that BD patients with alcohol use disorders had longer delays from onset of affective symptoms to treatment with mood-stabilizers (Goldberg & Ernst, 2002).

On the other hand, BD patients with more severe clinical presentations are more likely to seek help rapidly (ten Have et al., 2002) and also receive treatment faster (Baethge et al., 2003; Baldessarini et al., 2003; Goldberg & Ernst, 2002; Mantere et al., 2008) than patients with less severe symptomatology. In general, the odds for patients with co-occurring mental and substance use disorders using health services are higher than for patients with a single disorder (Jacobi et al., 2004; Regier et al., 1993; Urbanoski et al., 2007; Wu et al., 1999). Taken together, there are indications that the presence of comorbid SUD may be associated with both longer *and* shorter treatment delays in BD patients. These discrepancies may also be related to whether the substance abuse appears before or after the onset of the first BD episode. If the first BD episode starts before the substance abuse, treatment delay may increase the risk for substance use as self-medication of mood symptoms.

Self-medication as a possible consequence of treatment delay

The self medication hypothesis originally proposed by Khantzian in 1985 postulated that specific substances are used in order to alleviate particular painful affects (Khantzian, 1985). In a later reconsideration of the hypothesis, the author also claims that self-medication occurs because of “difficulties in regulating affects, self-esteem, relationships and self care” (Khantzian, 1997), but maintained the notion that a drug may be especially appealing to an individual due to his/her personality organization and specific psychological suffering. There is little or no evidence that specific substances are associated with specific psychiatric disorders, nor is it clear that patients with BD selectively use substances to match their affective phase. Some findings, however, indicate that the latter may be the case. In a prospective study, alcohol use was found to be more prevalent during depressive episodes and cannabis use more prevalent during manic episodes (Baethge et al., 2008).

Another model incorporating the idea of self-medication is the “stress-coping model” of addiction, which suggests that substances are used both to reduce negative affect and increase positive affect (Shiffman & Wills, 1985). In the realms of BD, where affective instability is the cornerstone, this model seems to have high face validity. Closely related to this hypothesis is the “alleviation of dysphoria” model. This suggests that humans use substances to ease dysphoric mood, and because individuals with severe mental disorders are especially prone to dysphoric experiences they are also more prone to use psychoactive substances (Mueser et al., 1998). There are several studies supporting the notion that patients with BD use substances to alleviate mood symptoms. In a clinical study, patients with BD and SUD scored higher on the self-medication items of a self-report measure compared to BD patients without SUD (Bizzarri et al., 2007). In an

epidemiological study, 41% of the patients with BD reported to have used substances to relieve mood symptoms in one or more affective episodes (Bolton et al., 2009). In a qualitative study patients reported that they used substances both to cope with depression and to alleviate symptoms of elation (Healey et al., 2009).

For patients experiencing long treatment delays, the likelihood of developing excessive substance use may increase as a consequence of an escalating need of symptom alleviation. Whether patients without initial excessive substance use that experience long treatment delays have an increased risk of developing excessive substance use has to my knowledge not yet been investigated.

1.5 Synopsis and introduction to aims

Individuals with BD often abuse psychoactive substances. To what extent BD patients without SUDs use substances (excessively or occasionally), is sparsely investigated. Furthermore, although the rates of SUDs among patients with BD are generally high they also vary widely. As substance use varies across cultures and geographical areas, the prevalence of substance use in a BD population should be compared to the prevalence in the general population of the same geographical area.

To what degree and in which outcome areas substance abuse and -dependence have a negative impact on the BD are research questions that have given diverging answers so far. Thus, further research conducted on well characterized and representative patient samples is needed, both to clarify which characteristics are associated with excessive substance use and how strong these associations are.

During the recent years, there has been increasing focus on the age at onset of BD. Variation in age at onset has been associated with several factors, including substance abuse. However, the relationship between age at onset, type of substance use and sequencing of the onsets of BD and excessive substance use calls for further investigation.

Research has shown that the delay between the onset of BD and a correct diagnosis and adequate treatment is long. How this delay is related to excessive substance use is sparsely investigated. When excessive substance use precedes the onset of the BD, it may both delay and expedite treatment initiation. When patients experience long delays from onset of the BD until treatment initiation, this may also increase the risk of excessive substance use as an attempt to self-medicate increasing symptoms.

The focus of this thesis is the relationship between excessive substances use and central aspects of BD; the development or onset of the disorder, the clinical and functional characteristics, and the initiation of adequate treatment.

2 AIMS OF THE THESIS

The main objective of this thesis was to gain more knowledge on the relationship between excessive substance use and BD, with special focus on age at onset, treatment delay and outcome. To obtain this, the following research questions were addressed in the individual papers:

Paper I:

- 1) Is the rate of lifetime use of illicit substances higher in the patient sample than in the reference population?
- 2) Do patients with and without excessive substance use, defined as substance use disorders and/or excessive use, differ on clinical and functional characteristics, in terms of disease course variables, current symptom levels and functioning?

Paper II:

- 3) Does the age at onset of the bipolar disorder differ between patients with excessive alcohol use, excessive cannabis use and patients using neither substance?
- 4) Does type of excessive substance use (alcohol, cannabis) and sequencing (of the onset of excessive substance use and the bipolar disorder) independently predict age at onset after adjusting for possible confounders?

Paper III:

- 5) What are the predictors of treatment delay, and is there a difference in *primary BD* (no excessive substance use preceding the first BD episode) and *secondary BD* (excessive substance use preceding the onset of the first BD episode)?
- 6) Within the *primary BD* group, do long treatment delays increase the risk of later excessive substance use?

3 MATERIAL AND METHODS

3.1 *Setting*

The current study is part of The Thematically Organized Psychosis (TOP) study. This is a large collaboration between the University of Oslo, Oslo University Hospital (formerly Ullevål University Hospital, “Rikshospitalet” and Aker University Hospital), Lovisenberg - Diakonhjemmet Hospital, and two large hospitals outside of Oslo. The project has a translational approach, aiming at gaining more knowledge on clinical, biological and environmental aspects of BD, schizophrenia and related psychiatric disorders. Patient inclusion started in October 2002 and is still ongoing. The TOP study aims at recruiting all patients within the relevant diagnostic groups that are being treated in public psychiatric services. To aspire to do this, the recruiting personnel collaborates closely with the clinical staff in the psychiatric units. The current study is cross-sectional and naturalistic. The project is approved by the Regional Committee for Medical Research Ethics as well as the Norwegian Data Inspectorate, and the data file received an Audit Certificate from the Center for Clinical Research at Ullevål University Hospital in 2007.

3.2 *Material*

Patients included in the current study were recruited from the psychiatric units (in- and outpatient) of the three major hospitals in Oslo from 2003 - 2008. Patients with a DSM-IV BD I, II or NOS diagnosis were recruited. Participants were excluded if they had a history of moderate/severe head injury, neurological disorder, developmental delays, an age outside of 18–65 years, or if they did not speak a Scandinavian language. Patients were referred to the project by their treating clinician after an evaluation of their eligibility and ability to give informed consent. The clinical interviews were conducted by research fellows who were trained clinicians (M.D.s or clinical psychologists). Informed consent was signed before the interview started. In some cases, the inclusion process was started while the patient was hospitalized. However, to ensure that patients were symptomatically stable and able to give informed consent, most of the assessments took place in out-patient clinics.

The patient sample of paper I consists of 125 patients included from 2003 to 2007. An additional 26 patients were included until August 2008 and added to the original sample, comprising the patient sample of paper II and III. In the total group of 151 patients, 88 (58.3%) had BD I, 57 (37.7%) BD II and 6 (4%) BD NOS. The 6 BD NOS patients were for the data analyses recoded as either BD I or BD II depending on the presence of mania or hypomania in their illness

history. Other sociodemographic and clinical characteristics of this sample are presented in Table 2. The 26 patients that were lastly added did not differ significantly from the original sample on any relevant measures.

Table 2. Total sample sociodemographic and clinical characteristics.

	Total sample N=151[#]
Gender, female, n (%)	92 (60.9)
Age, years, mean (SD)	35.9 (11.8)
Ethnicity, Caucasian, n (%)	139 (92.1)
Marital status, married/living as married, n (%)	49 (32.5)
Years of education, mean (SD)	14.5 (3.0)
Age at first affective episode, years, mean (SD)	22.7 (9.3)
Duration of illness, years, median (IQR)	11 (15)
Lifetime use of illicit drugs, n (%)	100 (66.2)
Substance use disorder*, n (%)	47 (31.1)
Excessive substance use*, n (%)	19 (12.6)
Age at onset of SUD or excessive substance use, years, mean (%)	23.5 (10.1)
Hospitalized (lifetime), n (%) [#]	103 (68.2)
No. of hospitalizations, median (IQR)	1 (3)
Lifetime psychotic symptoms, n (%)	71 (47)
Lifetime adequate pharmacological treatment, n (%)	108 (71.5)
GAF S, mean (SD)	56.5 (10.9)
GAF F, mean (SD)	53.6 (11.7)
IDS-C, median (IQR)	14 (18)

SUD=Substance use disorder. GAF S=Global Assessment of Functioning Scale, symptom subscale. GAF F=Global Assessment of Functioning Scale, Functioning subscale. IDS-C=Inventory of Depressive Symptoms, Clinician rated.

[#]in which the original sample of 125 patients is included

*Lifetime, of at least one substance. Patients with both SUD and excessive use are only coded with SUD.

[#]3 missing

In paper I, a sample from the general population collected by the Norwegian Institute for Alcohol and Drug Research (SIRUS) was used as a reference group. SIRUS regularly conducts surveys of the Norwegian population's consumption of illicit substances by personal interviews via standardized questionnaires. Sampling strategies are used to ensure random sampling and thus representativity. In the present study, SIRUS data from Oslo in 2004 was used (Horverak & Bye, 2007). For matching purposes, participants aged 18-65 were selected, leaving a representative sample of 327 subjects.

3.3 Methods

3.3.1 Diagnostic assessment

Diagnoses were established using the Structured Clinical Interview (SCID) for DSM-IV, modules A-E (First et al., 1995). All interviewers were trained based on the training program at UCLA (CA, USA) and participated in regular diagnostic consensus meetings. A good inter-rater reliability based on the UCLA training procedure was achieved with an overall kappa score of 0.77 (95% CI: 0.60-0.94). To assess reliability for actual study interviews a stratified random sample was drawn, consisting of cases from most of the assessment staff members. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. For the 28 vignettes the overall agreement for the nine DSM-IV diagnostic categories was 82% and the overall Kappa again 0.77 (95% CI: 0.60-0.94).

3.3.2 Assessment of sociodemographic characteristics, symptoms and illness course

Data were collected regarding age, gender, ethnicity, marital status, education, occupational status, family history of psychiatric disorders including substance abuse, history of suicide attempts, - psychosis, - psychiatric hospitalizations and psychopharmacological medication, age at onset of affective episodes, and age at first contact with specialized psychiatric care. This information was cross-checked with medical charts and information from interviews with close family members if relevant. Patients were considered to have had a lifetime psychosis if they had one or more SCID-verified psychotic episodes. A family history of depression, BD, schizophrenia, and other psychotic disorders among first degree relatives (i.e. mother, father, brothers and sisters) was obtained through patient interviews. Patients having a minimum of one first-degree relative with one or more psychiatric disorders were considered to have a family history. A family history of psychotic disorders other than BD was considered since several recent studies have shown common heritability for BD and schizophrenia (Craddock et al., 2009; Lichtenstein et al., 2009).

Depressive symptoms were assessed with the Inventory of Depressive Symptomatology (IDS-C) (Rush et al., 1996), (hypo)manic symptoms with the Young Mania Rating Scale (YMRS) (Young et al., 1978), general non-psychotic symptoms by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and current functioning by the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976), split version (Pedersen et al., 2007). The Medication Adherence Rating Scale (MARS) (Thompson et al., 2000) was used to measure compliance to medication. Increasing GAF scores signify fewer symptoms or better functioning, while for the remaining symptom scales,

higher scores signify more symptoms. The reliability for the PANSS general subscale was good, with an intraclass correlation coefficient (ICC) of 0.73 (95% CI: 0.54-0.90). The ICC was 0.86 (95% CI: 0.77-0.92) for GAF-S and 0.86 (95% CI: 0.77-0.92) for GAF-F.

3.3.3 Excessive substance use assessment and definitions

Substance use disorders were diagnosed through the SCID E-module. Each patient also reported lifetime substance use (daily, weekly, monthly, or occasional/no use) for all substances for the following life periods: 11-15 years, 16-20 years, 21-27 years, 28-44 years, 45-60 years, and 60+ years. (Appendix, Table 2). The intervals were based on the possibility of different use patterns and differences in the pathophysiological influence of substances across different life periods. The lifetime substance use evaluation is administered as an interview, where the scores are based on the clinician's evaluation of the patients' reports. When a specific use period did not correspond with a defined period, it was coded in the period with the greatest overlap. The frequency coded was also the average or predominant frequency within a period; "weekly" could be less than weekly for a sub-period if it was also equivalently more than weekly within the same period. Predominantly *daily* use of alcohol and predominantly *weekly* use of a non-alcoholic substance throughout at least one of the life periods (i.e. minimum 4 years) were considered excessive.

Structured interviews about the consumption of substances the last 6 months were also conducted; alcohol use was assessed by number of units and illicit substances by number of incidents. Different non-alcoholic substances were asked for specifically and the use was quantified by totaling the number of incidents recalled. When units or incidents were too frequent for precise recall, effort was put into identifying typical periods of mean weekly use and adding up by number of weeks for that period. Data on incidents of use past 6 months were pooled for all non-alcoholic substances, and specific incidents for each drug were not recorded unless only one type of drug had been used. There were no statistically significant differences regarding the number of units of alcohol or number of incidents of use of non-alcoholic substances consumed the last 6 months between patients fulfilling SUD criteria and patients with excessive use (Table 4). But these two groups combined differed significantly from the group with neither SUD nor excessive substance use regarding use of alcohol and illicit substances the last 6 months (Table 5). Thus, in the current study, excessive substance use was defined as substance use either fulfilling lifetime SUD or excessive use criteria. Age at onset of excessive substance use was deemed to be either 1) the age when DSM-IV SUD criteria were first met, or 2) the age when the patient started daily use of alcohol or weekly use of a non-alcoholic substance(s).

Table 4. Consumption of alcohol and illicit drugs the last 6 months for patients with substance use disorders versus excessive use.

	Patients with SUD	Patients with excessive use	Test statistics
Units of alcohol, median (IQR)	75 (399)	130 (398)	U=313.00, p=0.55
Incidences of illicit drug use, median (IQR)	0 (4)	0 (12.5)	U=290.00, p=0.65

SUD=Substance use disorder.

IQR=Interquartile range. U=Mann Whitney U-test.

Table 5. Consumption of alcohol and illicit drugs the last 6 months for patients with substance use disorders or excessive use versus patients with neither.

	Patients with SUD or excessive use	Patients with neither	Test statistics
Units of alcohol, median (IQR)	121 (394)	36 (106)	U=1365, p=0.037
Incidences of illicit drug use, median(IQR)	0 (5)	0 (0)	U=1448.5, p=0.001

SUD=Substance use disorder.

IQR=Interquartile range. U=Mann Whitney U-test

Excessive use of alcohol versus cannabis

In paper II, patients with excessive alcohol use, excessive cannabis use and patients without such excessive use were compared. Twenty-eight patients (19%) had excessive alcohol use, 24 patients (16%) had excessive cannabis use, and 11 patients (7%) used both substances. Patients who used both were similar to the patients who used cannabis only and not to the patients who used alcohol only for all relevant clinical and sociodemographic characteristics, and were therefore grouped together with the cannabis-only patients in the bivariate analyses for research question 1. But to further ensure that the differences between the alcohol and cannabis groups were not due to the characteristics of the patients using both alcohol and cannabis, follow-up analyses were conducted excluding these patients. These analyses did not indicate any changes in the group wise differences for age, AAO and age at onset of excessive substance use, or for the proportion with BD I or a family history of affective/psychotic disorder compared to the original analyses. The difference in the proportion with excessive use of other substances was, however, no longer significant (18% vs. 25%, $\chi^2=0.40$, $p=0.53$) implying that excessive polysubstance use was a characteristic of the excluded group. Among the 88 patients with neither excessive alcohol nor cannabis use, three patients (3%) had excessive use of other substances. These 88 patients are subsequently referred to as non-users.

3.3.4 Temporal sequencing

In paper II, AAO was defined as the age when the first SCID-verified affective episode began. In paper II and III the patients were divided into two subgroups determined by the presence or absence of excessive substance use preceding the first affective episode: *primary BD* were patients with no excessive substance use preceding the first affective episode, and *secondary BD* were patients with onset of the first affective episode after the onset of excessive substance use. This dichotomous variable is subsequently referred to as the *sequencing* of onsets. The small group of patients (n=6) with onsets of both within the same year was categorized as secondary BD. This was done because excessive substance use to a greater degree than BD has a gradual rather than an abrupt onset. Since all patients in this study eventually were diagnosed with BD, affective episodes associated with substance use in patients with no previous BD episode were used as markers for the AAO. Using these criteria, 117 patients had primary BD (77%) and 34 (23%) had secondary BD. Patients with primary BD could develop excessive substance use after the onset of BD, and data showed that 32 patients (21% of all patients) subsequently did.

3.3.5 Treatment delay

Several definitions have been used to define the onset of BD: First affective symptoms (Goldberg & Ernst, 2002; Morken et al., 2009; Post et al., 2008), first affective episode according to diagnostic criteria (Larsson et al., 2009; Oedegaard et al., 2009; Suominen et al., 2007), first medical contact because of the BD (Baethge et al., 2003) and time of first psychiatric intervention (Baldessarini et al., 1999; Baldessarini et al., 2003). Also, at least two different definitions of treatment start have been used: First contact with psychiatric care irrespective of mood disorder diagnosis (Suominen et al., 2007) and first treatment with a mood-stabilizer (Goldberg & Ernst, 2002). There is thus no consensus in the field on the definition of BD treatment delay that parallels the concept of “duration of untreated psychosis” used in studies of psychotic disorders (Melle et al., 2004). For the purpose of the health service focus of research question 5 (paper III), the start-point was defined as the first time it was possible to give the BD diagnosis – i.e. the onset of the first SCID-verified elevated episode (hypomanic, manic or mixed). For the purpose of the clinical focus of research question 6 (paper III), the onset of the first SCID verified affective episode regardless of polarity was defined as the start-point. The end-point was for both research questions defined as age at first mood-stabilizing or antipsychotic medication, defined as appropriate dosages for at least 6 weeks in line with available treatment guidelines for BD (Goodwin, 2009; Grunze et al., 2004). The treatment delay variable was highly skewed and could not be transformed into a normal

distribution by any form of transformation and was thus dichotomized into short and long delay by the median value of 2 years (short delay ≤ 2 years, long delay > 2 years).

3.4 Statistical analyses

All analyses were done using the Statistical Package for the Social Sciences (SPSS) version 16.0 (Inc., Chicago, IL, USA). Statistical significance was determined using the .05 level and 2-tailed tests of significance. Chi-square tests and Fisher's exact tests were used when investigating group differences on categorical data. Group differences in independent samples were explored with Student's t-tests and ANOVAs (with Tukey's post-hoc tests) on normally distributed continuous variables and Mann Whitney U-tests and Kruskal Wallis tests for variables with skewed distributions. The distribution of skewed variables is presented through medians and interquartile ranges (IQR). Bivariate associations between continuous dependent and independent variables were assessed with Pearson correlations when variables were normally distributed and Spearman rank correlations when variables were skewed. The Kaplan-Meier Survival Analysis was used for comparing groups on time in remission. Binary logistic regression analyses were used to investigate the relationship between a dichotomous dependent variable and multiple independent variables. Hierarchical multiple regression analyses were used to investigate the relationship between one continuous dependent variable and multiple independent variables. The two-way ANOVA was used to investigate possible interactions between variables. Possible confounders were chosen on the basis of associations found in bivariate analyses and findings from earlier studies. For concrete details on statistical analyses in each of the substudies, the reader is referred to the papers.

4 RESULTS AND SUMMARY OF PAPERS

Paper I: Excessive substance use in bipolar disorder is associated with functioning rather than clinical characteristics, a descriptive study

Background: There is a strong association between BD and SUD. The clinical and functional correlates of SUD in BD are still unclear and little is known about the role of excessive substance use that does not meet SUD criteria. Thus, the aims of the current study were to investigate lifetime rates of illicit substance use in BD relative to the normal population and if there are differences in clinical and functional features between BD patients with and without excessive substance use.

Methods: 125 consecutively recruited BD in- and outpatients from the Oslo University Hospitals and 327 persons randomly drawn from the population in Oslo, Norway participated. Clinical and functional variables were assessed. Excessive substance use was defined as DSM-IV SUD and/or excessive use according to predefined criteria.

Results: The rate of lifetime illicit substance use was significantly higher among patients compared to the reference population (OR=3.03, CI=1.9-4.8, $p<.001$). Patients with excessive substance use (45% of total) had poorer educational level, occupational status, GAF-scores and medication compliance, with a trend towards higher suicidality rates, compared to patients without. There were no significant group differences in current symptom levels or disease course between groups.

Conclusion: The percentage of patients with BD that had tried illicit substances was significantly higher than in the normal population. BD patients with excessive substance use clearly have impaired functioning, but not a worse course of illness compared to patients without excessive substance use. An assessment of substance use beyond SUD criteria in BD is clinically relevant.

Paper II: Excessive cannabis use is associated with earlier age at onset compared to excessive alcohol use in bipolar disorder

Background: Several factors appear to be associated with variation in age at onset in BD, substance use being one. How different substance types and differences in the temporal relationship between the onset of BD and the onset of substance use are related to age at onset is unclear. The aim of the study was to investigate which factors are associated with age at onset in bipolar disorder with a specific focus on excessive alcohol and cannabis use, and the sequence of the onsets of excessive substance use and bipolar disorder.

Methods: We investigated a naturalistic sample of 151 patients with bipolar I and II disorder receiving psychiatric treatment. Whether the presence of excessive substance use prior to bipolar disorder onset or the type of substance used (alcohol or cannabis) was associated with differences in age at onset was investigated using hierarchical, multiple linear regression analyses, adjusting for potential confounders.

Results: Patients with excessive alcohol use had a significantly later onset compared to patients with excessive cannabis use. Excessive general substance use prior to bipolar disorder onset was associated with a later onset. However, excessive cannabis use was associated with an earlier onset whether it preceded or followed bipolar disorder onset, also after adjusting for possible confounders. Excessive use of alcohol or other substances was not independently associated with age at onset in multivariate analyses.

Conclusions: Alcohol use was associated with a later onset compared to cannabis use, suggesting different relationships to the onset of bipolar disorder. Lifetime use of cannabis was associated with an earlier onset, independent of the sequence of onsets. This indicates that an early onset may increase the risk of cannabis use and that cannabis use may trigger bipolar disorder in vulnerable individuals.

Paper III: Treatment delay and excessive substance use in bipolar disorder

Background: The delay between illness onset and adequate pharmacological treatment in BD is often long. How treatment delay is related to excessive substance use has been sparsely investigated. The objective of the present study was to investigate whether excessive substance use before illness onset is associated with increased or reduced treatment delay, and whether long treatment delays are associated with increased risk for subsequent excessive substance use.

Methods: 151 BD I and II patients were consecutively recruited from in- and outpatient psychiatric units, and categorized as primary or secondary BD (with or without antecedent excessive substance use). Predictors of treatment delay among all patients, and predictors of subsequent excessive substance use among primary BD patients, were investigated with logistic regression analyses.

Results: The median treatment delay was 2.0 years (IQR 14.0). The risk of a long treatment delay (>2 years from first elevated episode to adequate pharmacological treatment) was increased in patients with BD II disorder, no lifetime psychosis, a higher age at first contact with specialized

psychiatric services, primary BD and excessive substance use. In primary BD, the risk for developing excessive substance use was increased in males, in patients with shorter education and longer treatment delays.

Conclusion: Patients with antecedent excessive substance use had reduced risk of long treatment delays. The risk of developing excessive substance use after BD onset increased with longer treatment delays.

5 DISCUSSION

5.1 *Methodological issues*

5.1.1 Sample representativity

The current study is based on a sample recruited in a publicly funded, catchment-area organized health care system with no alternative treatment facilities (e.g. private clinics). The cost carried by each patient receiving outpatient health care and/or prescribed drugs is limited to a fixed amount (NOK 1840 (EUR 228) per year), and access to in-patient care is free. In areas where health service utilization and access are partly governed by external factors such as cultural preferences (e.g. treatment in a university clinic is considered the most up-to-date) or lack of public funding (e.g. the only way to receive treatment is to participate in research), there is a risk of selecting patients that are not representative of the total population of treatment-seeking individuals. Some of the leading and most influential studies on BD may be biased due to such preselection. In the sample of the present study, the risk of preselection is minimal, since patients participating in health care based research in Norway are likely to spread across all socio-economic and -cultural categories. The TOP study sample is also examined within a time interval of approximately five years, assuring concordance in time for variables susceptible for rapid changes within any given society (such as illegal drug use).

The aim was to include all eligible patients in treatment for the relevant diagnoses. Patients were recruited from both in- and outpatient units including substance abuse clinics. However, some potential biases need to be considered: Patient inclusions were based on referrals from their treating clinicians, and thus depended on the clinicians' understanding and good-will towards the aim to include all eligible patients. To ensure this, the TOP interviewers were based in one or two clinics, together covering all sites. They attended regular meetings to inform new staff members, remind all that patient inclusion was ongoing, and discuss possible cases. Clinicians may however have been skeptical towards research in general or "protective" on behalf of patients they considered fragile or severely ill. The impression was however that the possibility to receive a written report from state-of-the-art assessments outweighed potential skepticism. Furthermore, since the assessment period ran across several years, most patients were likely to be targeted in stable phases of their illness. Some clinicians may also have lacked the experience needed to identify the right patients. Research has documented that BD is often misdiagnosed (Hirschfeld et al., 2003). The impression was however that the diagnostic service offered by the TOP interviewers often was used as a second opinion in complicated or potential cases. Thus, in our opinion there

are few clear indications that the referral procedures have caused significant biases. We however do not have any information on the number or characteristics of eligible patients that were not referred due to the reliance on clinicians to do the initial screening.

One may also question whether the sample could be biased due to patients declining to participate after referral. Patients with severe forms of BD such as rapid cycling or chronic depressive courses may have declined more often than patients with less severe symptomatology. However, as described above, patients were asked again when symptom load was attenuated. Another possible excluding factor may have been that patients that had never experienced psychosis would be reluctant to participate in a project named “Thematically Organized Psychosis Study”. However, the project name was known by most patients in its abbreviated form “TOP”, and patients with non-psychotic BD would be informed by both their clinician and the interviewer that they were eligible. The proportion with psychotic symptoms in the current study was 47% (Table 2), which is similar to findings from other clinical studies on BD (Mantere et al., 2004; Mitchell et al., 2009). Thus, there does not seem to be a bias towards psychotic BD in the present material.

Furthermore, some patients may have perceived the assessment as too extensive. In such cases, patients were encouraged to participate in as many assessments as they wanted rather than to decline. The vast majority of cases participated in all baseline assessments, indicating that the total burden was regarded as acceptable by most patients. As in all research projects, a bias towards patients with a positive attitude towards research could be assumed. This is however likely to be related rather to the fact that some patients are more easily recruited to research than others, than to the specific design of the current study. Information regarding patients declining to participate in the study could not be accessed due to the person data security act.

In order to investigate the representativity of the patients included in the TOP Study, data were compared with accessible variables from the Ullevål 600 Health Care Study. This is a survey conducted during the first years of recruitment in the TOP Study on all patients from the Department of Psychiatry at the former Ullevål University Hospital (constituting the largest and most heterogeneous health care sector in Oslo), comprising a total of 1002 subjects with psychoses and severe BD. These comparisons show that the TOP patients are representative for the clinical population as a whole on variables such as socioeconomic status, level of education, and substance use. The mean age of the current study’s sample was slightly lower compared to the Ullevål 600 Study: 35.9 (11.8) versus 39.2 (12.8) years.

The mean age at onset of the BD in the current sample was 22.7 years, and age at onset and age at assessment were moderately correlated ($r=0.52$). Thus, this is a fairly young sample with relatively short illness duration, i.e. consisting of few chronic patients. Twenty-eight percent of the

patients had not yet received adequate pharmacological treatment, suggesting that they were either recently referred to treatment, or had a relatively low level of symptoms. The majority of patients were also recruited from out-patient clinics.

The patient sample of the current study is not an epidemiological sample, which probably would have included more cases with very benign forms of BD and cases that chose not to have contact with treatment services or fail to comply with specialized treatment (e.g. attending appointments). There are however many indications that the sample of the current study consists of patients representative of an unselected treatment-receiving population of patients with BD. Due to the varying quality of epidemiological studies on the prevalence and incidence of BD, it is difficult to estimate how close the number of patients included in the present study is to the actual number of individuals with BD in the catchment area covered.

5.1.2 Reliability and validity of assessments

The instruments employed to assess diagnoses, symptoms, and level of functioning in the TOP Study are widely recognized and utilized in clinical psychiatric research. It is well documented that the SCID-I interview in general may yield highly reliable diagnoses (Segal et al., 1994), and it is considered to be the gold standard of diagnostic assessment. The Inventory of Depressive Symptoms, Clinician Rated (IDS-C) has a more complete item coverage compared to other frequently used measures of depressive symptomatology, and has satisfactory psychometric properties (Rush et al., 1996). The Young Mania Rating Scale (YMRS) with its good psychometric properties (Young et al., 1978) is often regarded as the gold standard for assessment of manic symptomatology (Poolsup et al., 1999). The Positive and Negative Syndrome Scale (PANSS) is developed for schizophrenia, but has been used in previous studies on BD without encountering significant validity problems (Daneluzzo et al., 2002). The GAF Scale constitutes the axis V of the present DSM-IV diagnostic system, and has achieved worldwide status as a primary instrument for assessing change in psychiatric symptoms and functioning. Although its reliability in clinical settings has been questioned, especially the split version, it has proven highly satisfactory in research settings (Pedersen et al., 2007; Vatnaland et al., 2007).

Reliable ratings in the use of all clinical measures in the TOP Study were ensured in several ways. Firstly, all interviewers were experienced clinicians, and went through standardized education and training on all clinical instruments. The interviewers had biweekly supervision including reviews of ongoing clinical interviews, and participated in monthly diagnostic supervision meetings led by a senior clinician/scientist. Furthermore, inter-rater reliability tests were

conducted for the SCID, PANSS and GAF assessments and showed very good to excellent results (for details, see methods section).

Retrospective gathering of data on the development of symptoms and drug use implies the possibility of recall bias. Information on illness history was therefore cross-checked with case files, and with family members if it appeared conflicting or deficient, which could be the case e.g. when illness history was long or insight in symptoms low. Self-report of substance use in patients with BD has previously been shown to have a high degree of validity, especially when urine samples are also collected with the patients' prior knowledge (Weiss et al., 1998). This was the case in the current study, and urine samples corresponded well (in 90% of the cases) with patients' own reports of consumption of non-alcoholic substances in the previous weeks (Ringen et al., 2007). To further ensure that substance use was not under-reported, we gave patients the opportunity to have such information excluded from the reports sent to the treating clinician to avoid potential negative consequences. A few patients chose to report drug use only on this precondition. The lifetime substance use measure used to assess excessive substance use in the present study (Appendix, Table 2) was designed by collaborators in the TOP Study, and has not been tested for validity and reliability. However, it is a straight-forward measure of frequency of substance use with high face validity and relatively little room for interpretation (see methods section). SIRUS used phone interviews to collect information on drug use, which have disclosure rates similar to in-person-interviews and paper-and-pencil questionnaires, and the advantage of higher participation rates (Rosenbaum et al., 2006).

Using patients' reports to record family history of psychiatric diagnoses has some limitations, including relatively poor sensitivity and specificity (Roy et al., 1996). A more reliable method would have been conducting diagnostic interviews with all first degree relatives. However, compared to other Norwegian cities, Oslo has a high proportion of inhabitants that have relocated from other cities, which would make such interviews very resource-intensive. Furthermore, a meta analysis of the psychometric properties of patient's reports of family history yielded relatively high reliability and validity for schizophrenia, mania and substance abuse (as opposed to for anxiety, depression and personality disorders) (Hardt & Franke, 2007). These disorders constitute the majority of the disorders of interest in the current study.

5.2 Ethical considerations

Although the project's ethical aspects are officially approved, and all patients participating in the study signed informed consent, some ethical issues should be addressed. In patients with psychiatric symptoms that may interfere with reality testing, the concept of informed consent

involves special challenges. Therefore, the patient's psychiatric condition was thoroughly evaluated by their treating clinician and the research fellow in collaboration before the patient was asked to participate. The way the information about the study was communicated was individually adjusted; some patients needed to have the information on more than one occasion before assessments started. Patients were also explicitly told that they could, at any time, decline from the study, and that this would not have any consequences for their treatment in the clinic. The collaboration with the clinicians also ensured that participation in the study did not interfere with the treatment.

Parts of the patient data on which this study is based, is highly personal and sensitive and thus emotionally loaded. In addition to working to obtain an empathetic atmosphere during the interviews, the assessments were often broken up into several sessions on different days. The interviews were carried out at either at the clinic or in the research offices, according to the preference of the patient. In addition to the clinical interviews, blood and urine sampling, somatic-, neuropsychological- and brain imaging- assessments were carried out. The total load on each participant may be compared to a thorough clinical evaluation. When needed, patients were offered taxi transportation for the appointments.

When assessments were completed, reports from the neuropsychological testing and the clinical interview were written and sent to the treating clinician with the patients consent. Patients were also offered an appointment with the interviewer with the treating clinician present where the information from the reports was presented orally and discussed. The general impression was that both the written reports and the feed-back appointments were highly appreciated as useful by both the clinician and the patient.

5.3 Discussion of main results

5.3.1 The prevalence of lifetime illicit substance use in bipolar disorder

Sixty-five percent of the patient sample and 40% of the general population sample had lifetime use of illicit substances. Statistical analysis indicates that this implies a threefold risk in patients compared to the general population. This suggests that the risk is greater in BD than in the general population not only to develop excessive substance use, but also to use illicit drugs. The (hypo)manic symptom of "excessive involvement in pleasurable activities" may involve experimenting with drugs. However, several studies have found increased impulsivity and novelty seeking even in euthymic BD patients (Nery et al., 2008; Swann et al., 2001), and these traits have also been linked to substance use (Brady et al., 1998; Fergusson et al., 2008). Another model proposed to account for the propensity to substance use in BD is a hypersensitive "Behavioral

Approach System" (BAS). The BAS is conceptualized as a psychobiological system regulating approach to reward or appetitive stimuli (Depue & Iacono, 1989). BAS sensitivity has been linked to an increased risk of (hypo)manic episodes (Alloy et al., 2008), and a prospective study showed that high BAS sensitivity predicted SUDs in a sample of BD patients (Alloy et al., 2009). The authors hypothesize that these characteristics represent shared vulnerability factors for BD and SUDs. The findings on impulsivity, novelty seeking and BAS sensitivity in BD may explain our results showing an increased propensity towards substance use even among patients that have not developed excessive substance use.

5.3.2 The relationship between excessive substance use and the outcome of bipolar disorder

Our results did not give many indications that the presence of excessive substance use was associated with more a more severe course of the BD. There were however several indicators of a poorer functioning in the excessive substance use group compared to the no use group, including shorter education length and lower employment rates. Although earlier studies are inconsistent, our findings of poorer functioning in the excessive substance use group are in line with several studies showing increased occupational impairment (Haro et al., 2006; Tohen et al., 1990), reduced educational level (Sonne et al., 1994; Weiss et al., 2005) and worse global functioning (Cardoso et al., 2008; O'Connell et al., 1991) associated with comorbid SUD. The excessive substance use group also had poorer compliance to medication, which is in accordance with earlier and more consistent findings (Manwani et al., 2007; Sajatovic et al., 2009). Whether relationships between substance use and impairment are due to negative effects from the excessive substance use, or the impairment was present before the excessive substance use developed (and thus may instead comprise risk factors for substance abuse), cannot be determined on the basis of the present findings.

Indicators of disease severity in BD, such as current depressive or manic symptoms, number of affective episodes or BD type, did not differ between patients with or without excessive substance use. A possible explanation of the lack of associations between excessive substance use and current affective symptomatology is the fact that we investigated lifetime and not current excessive substance use; an unknown proportion of the patients may have recovered from their SUD or ceased using substances excessively when symptom assessment was conducted. However, we found that the consumption of both alcohol and drugs the last 6 months were higher in patients with excessive substance use compared to patients without, demonstrating that there were significant differences in recent substance use. Furthermore, the finding of no differences in

current affective symptomatology is in line with several other studies finding no differences across groups defined by SUD in these variables (Goldberg et al., 1999; Sonne et al., 1994).

We found no significant differences in measures of remission between patients with or without excessive substance use. This was unexpected, since prolonged affective episodes are found quite consistently by earlier research (Weiss et al., 2005). However, there were numerical differences between the groups in the expected direction on these variables, so this difference could reach statistical significance in a larger sample (i.e. findings may represent a type II error). Furthermore, the present finding of no relationship between excessive substance use and number of affective episodes is in line with previous research (Nolen et al., 2004) although this is sparsely investigated. Finally, the similar distribution of bipolar subtypes across the groups in our study converges with some studies (Weiss et al., 2005), but is contrary to those finding higher SUD rates in bipolar I disorder compared to bipolar II disorder (Chengappa et al., 2000; Regier et al., 1990).

Our findings of no differences in BD illness severity between patients with or without excessive substance use is in accordance with a study on BD I disorder with or without SUD for several proxies for BD severity (Goldstein & Levitt, 2008). It also converges with the findings of a recent study where no differences in clinical characteristics were found between patients with a low, medium or excessive use of alcohol (van Zaane et al., 2010). The hypothesized potential for substance abuse to trigger BD in individuals with low constitutional vulnerability for the disorder (Strakowski et al., 2000; Winokur et al., 1998) could partly account for these negative findings: A lack of worsening of BD illness characteristics in the presence of SUD may be explained by a lower vulnerability for BD. Furthermore, according to the behavioral sensitization hypothesis, environmental factors such as substance use play a major role in the early course of the BD, while the further course is relatively independent from the influence of external factors (Post, 1992).

The trend towards increased suicidality rates, as well as the lower GAF S scores found in the excessive substance use group in the present study, could be signs of a poorer general psychiatric outcome that is not mediated by a more severe course of the BD. Increased suicidality is seen in a number of psychiatric disorders and has been found associated with SUD alone (Innamorati et al., 2008), and with the combination of SUD and a variety of psychiatric disorders (Bulik et al., 2008; Gentil et al., 2009; Limosin et al., 2007). Thus the increased suicidality may be more strongly related to the excessive substance use per se than to a more severe BD course. In summary, excessive substance use does not appear to be related to more severe specific BD illness characteristics, but to a more severe general psychiatric outcome in terms of worsening of unspecific and global clinical features frequently seen in association with SUDs alone (such as

poorer GAF symptom scores and increased suicidality). This may also be related to the burden of having two disorders.

5.3.3 The relationship between excessive alcohol and cannabis use and the age at onset of bipolar disorder

Excessive use of cannabis was associated with an earlier onset also after adjusting for potential confounders. Excessive alcohol users had a later onset, were older at assessment and had a later onset of the excessive use, a lower prevalence of family history as well as lower rates of use of other substances compared to the cannabis users. Our findings also suggest differences in sequencing: for the alcohol users, the mean AAO was earlier than the mean age at onset of the excessive substance use, while for the cannabis users the mean AAO was later than the mean age at onset of the excessive substance use. There was, however, no interaction effect between type of substance use and sequencing on AAO.

One possible explanation for the association between early onset and excessive cannabis use could be that it is a cohort effect, i.e. that people born in the last decades may be at greater risk for developing excessive cannabis use than patients born earlier due to changes in use trends or availability. However, since excessive cannabis use was associated with AAO also after adjusting for current age, cohort effects cannot explain the finding. Furthermore, excessive cannabis use was associated with an earlier onset after adjusting for possible confounders such as family history and excessive use of other substances. Excessive alcohol use was however not independently associated with AAO. The later onset in alcohol users compared to cannabis users, and the independent predictive effect of cannabis as opposed to alcohol on AAO, may indicate that different mechanisms are involved in the relationships between the development of BD and these two most frequently used substances. Although somewhat speculative, our findings may indicate that cannabis has potential to trigger BD, while alcohol to a greater degree is used to self-medicate mood symptoms.

The association between cannabis use and early onset in the current study was present even after adjusting for sequencing and thus appears to exist both when the excessive use develops before, and after the BD. This is in contrast to earlier findings of a later onset in BD secondary to cannabis compared to primary BD (with or without cannabis use disorder)(Strakowski et al., 2007). This discrepancy could be due to differences in methodology and sample characteristics. One explanation may be the high family history rates in our sample of excessive cannabis users, an area where no data were presented in the previous study. Higher family history rates may indicate high vulnerability for BD, which may interact with excessive cannabis use to

cause an early onset in these patients. The complex relationship between AAO, type of substance used, sequencing and family history should be further explored in a larger sample allowing comparisons of several subgroups.

Our findings also indicate that an early onset increases the risk of subsequently developing excessive cannabis use. This is in accordance with earlier findings of an association between early onsets and drug abuse (Perlis et al., 2004; Wilens et al., 1999), which may have several explanations. Some authors have proposed that patients with early onsets may share a common increased genetic vulnerability mediating both BD and excessive drug use (Lin et al., 2006). Family history did not independently predict AAO in the present study. However, the family history rates of affective/psychotic disorders among the cannabis users were high. Having a close family member with a severe psychiatric disorder in addition to experiencing affective episodes early in life may also represent a substantial psychosocial burden, leaving the patient at increased risk for illicit substance use.

When patients with or without excessive substance use were compared in paper I, we found no difference in AAO. However, differences appeared when patients were divided into primary and secondary BD, and grouped according to type of substance used. Thus, the association between excessive substance use and AAO appears to depend on which substances that are used, and whether the BD is primary or secondary to excessive substance use.

It may seem contradictory that excessive substance use is associated with the onset of the BD (Paper II), whilst it appears not to be associated with the symptoms or course of the BD (Paper I). This apparent divergence may be explained by the kindling/behavioral sensitization hypotheses, postulating that environmental factors play a major role in the early course of the BD which eventually “lives it’s own life” relatively independently from external events such as substance use (Post et al., 1986). Furthermore, relationships with clinical characteristics and excessive substance use may have been found in the present study if we had investigated cannabis use separately, as indicated by other studies (Strakowski et al., 2007; van Rossum et al., 2009).

5.3.4 Excessive substance use and the onset of bipolar disorder

Even though the potential to trigger BD in vulnerable individuals has been proposed for both alcohol and cannabis (Strakowski et al., 2007; Winokur et al., 1995), the potential of cannabis may be greater. This is in line with two recent studies of acutely ill patients with a broad spectrum of psychotic disorders, showing that cannabis abuse/dependence was associated with an earlier onset of the psychotic disorders after adjusting for abuse/dependence of other substances including alcohol (Gonzalez-Pinto et al., 2008; Öngür et al., 2009). Our findings indicate that the association

between an earlier onset and excessive cannabis use is present also in a pure BD sample. Furthermore, it is fairly well established that cannabis use is a risk factor for the development of psychosis/schizophrenia in the presence of other risk factors such as genetic vulnerability (D'Souza et al., 2009). The fact that schizophrenia and BD have many clinical features in common as well as overlapping pathophysiology (Murray et al., 2004) increases the plausibility that cannabis use may act as a risk factor even in BD. There is also growing evidence from prospective epidemiological studies that cannabis use increases the risk for developing manic symptoms and BD (Henquet et al., 2006; van Laar et al., 2007), while alcohol abuse seems to increase the risk for depressive rather than manic symptomatology (Baethge et al., 2008; Fergusson et al., 2009). Furthermore, in a recent study on prodromes of first manic psychotic episode, 68% of patients were found to have substance use disorders in the prodromal phase out of which 82% used cannabis (Conus et al., 2010).

The present finding that secondary BD (relative to primary BD) was associated with a later onset is highly consistent with earlier studies (DelBello et al., 1999; Falk et al., 2008; Feinman & Dunner, 1996; Fossey et al., 2006; Strakowski et al., 1996; Strakowski et al., 2005; Strakowski et al., 2007). We also demonstrate that this effect remains significant even after adjusting for several variables known to be associated with AAO (gender, BD type, family history, type of substance used); further supporting the hypothesis that excessive substance use may trigger BD. We do not, however, replicate earlier findings that family history rates are lower in secondary BD compared to primary BD (DelBello et al., 1999). We do, however, demonstrate that the family history rates are higher among the cannabis users compared to the alcohol users and the non-users. Patients' reports of family history of psychiatric disorders is a somewhat crude measure (Roy et al., 1996), which may explain these inconsistencies. Furthermore, the full range of vulnerability markers and risk factors for BD are not yet known, thus other factors may have confounded this result.

5.3.5 The relationship between excessive substance use and treatment delay

We found that when excessive substance use preceded BD onset, the risk of a long treatment delay was reduced. This finding indicates that excessive substance does not appear to represent a barrier for receiving adequate pharmacological treatment in BD. This is in line with previous studies showing that patients with other co-occurring mental illness and SUDs are more likely to utilize health care services than patients with only one disorder (Jacobi et al., 2004; Regier et al., 1993; Urbanoski et al., 2007; Wu et al., 1999). Our finding also aligns with "Berkson's bias" showing that different disorders in the same individual independently influence help-seeking and need for care (Berkson, 1946), and thus accelerate treatment initiation in individuals with both BD and excessive

substance use. Furthermore, this finding converges with a recent study showing higher rates of SUDs in patients with recognized BD compared to patients with unrecognized BD (Mantere et al., 2008).

Focusing only on patients without excessive substance use at onset of the BD, we found that longer treatment delays were associated with an increased risk for developing excessive substance use. This risk was still present after adjusting for the influence of other predictors of substance use. Our finding here is thus in line with the self medication hypothesis (Khantzian, 1997) or the general “alleviation of dysphoria” model (Mueser et al., 1998), suggesting that psychiatric patients use substances as an attempt to deal with increasing symptoms or psychological distress. These theories have gained support from several other studies (Bizzarri et al., 2007; Bolton et al., 2009; Healey et al., 2009; Weiss et al., 2004). An alternative explanation of the association between treatment delay and subsequent excessive substance use is that substance using patients are more reluctant and less compliant with medication (Baldessarini et al., 2008; Goldberg et al., 1999; Keck, Jr. et al., 1998; Manwani et al., 2007). This appears less likely in the present study as there was no difference in the proportion that used medication in excessive substance users and non-users.

5.3.6 Strengths and limitations of the study

This is a study with a naturalistic design of BD patients in a catchment area-based specialized psychiatric treatment. Reliability-testing was performed for the most central assessments, and the patient sample was well characterized. The substance use assessments were particularly comprehensive.

The present study’s excessive substance use category is more broadly defined than DSM-IV SUDs, which have been the main focus in earlier studies. There is little knowledge about the appropriate cut-off for harmful substance use in patients with severe mental illness. Investigating a broader range of substance use than strict DSM-IV abuse or dependence in clinical studies on BD, such as the present study’s excessive substance use, may help to clarify this. Furthermore, considering excessive substance use based on frequency patterns and not only on harmful behavioral or psychological consequences (on which SUD criteria are based) adds to the current knowledge on substance use in BD. These advantages were considered to outweigh the disadvantages of using a substance abuse definition that diverges somewhat from previous studies. Also, there are several indications from the present study’s findings that excessive substance use is a valid category when investigating BD, such as its associations with functional characteristics, AAO

and treatment delay. Furthermore, the study demonstrates that patients with a frequent and sustained use of substances do not necessarily fulfill SUD diagnostic criteria.

The study has some limitations. The cross-sectional design does not provide direct information on causal relationships. Some of the same limitations apply to longitudinal naturalistic studies. However, the possibility to study the effects of psychoactive substances experimentally in humans is highly limited, due to the ethical issues related to exposure to potentially (and well known) harmful conditions. Cross-sectional naturalistic studies may give indirect indications of causal relationships, and challenge or support prevailing causal theories and -hypotheses.

Information on temporal relationships, i.e. what comes first and last, will give some information regarding what may possibly be either the cause or the effect. This is the idea behind using the primary and secondary BD categories (in paper II and III). There is however a risk for misclassification in these categories. The possibility of recall bias is of special relevance in this context, and has already been discussed. Furthermore, the onset of affective symptoms and excessive substance use may be intertwined. E.g. there may be cases in which the excessive substance use seems to be primary, however is used in a period of prodromal affective symptoms (and thus could have been classified as secondary). Using a diagnostic instrument specifically designed to determine the sequencing of psychiatric symptoms and substance use disorders such as the PRISM (Caton et al., 2000) could have facilitated more reliable classifications in some cases. This interview was however not available in a Norwegian translation at the time of the assessments for the current study. Furthermore, in cases where the development of the different symptoms is highly intertwined, even strictly operationalized criteria may not determine what is “truly” primary or secondary. In only 6 cases in the current study the excessive substance use and the first affective episode developed within the same year. Thus, these highly indeterminable cases thus do not constitute a great proportion of the total sample.

The sample in the current study was too small to investigate and compare some subgroups of interest. The relatively small sizes of the subgroups in both papers I and II imply a risk for type II errors. However, in paper I there are few substantial numerical differences between the groups, thus even a substantial increase in sample size would not lead to additional significant differences. In paper II, there are substantial differences between the groups in spite of the relatively small group sizes.

The current study did not include information on patient’s subjective experience with excessive substance use, e.g. rationale for using and perceived effect of different substances. Such information would have been valuable especially for clarifying questions regarding possible self-medication effects raised in paper III.

The findings regarding risk factors for treatment delay in paper III may be biased by the decision to dichotomize the treatment delay variable (\leq or > 2 years). However, the alternatives of using parametric statistics on a highly skewed variable or using non-parametric statistics (without the possibility for multivariate analyses) would most likely have generated less valid findings. Furthermore, all the identified predictors (except from the presence/absence of psychosis) were highly significant, thus appear to be relatively robust findings.

The end-point of treatment delay in paper III was defined as the initiation of adequate pharmacological treatment (defined as mood-stabilizing or anti-psychotic agents). This definition should not be interpreted as normative for a complete and satisfactory treatment for patients with BD, as there is growing evidence that psychotherapeutic interventions are crucial ingredients in the treatment of BD (Fountoulakis et al., 2009; Miklowitz & Scott, 2009). However, based on current knowledge of effective treatment of BD, it is considered to be the best single indicator of adequate treatment.

5.4 Theoretical implications

To what extent do the findings from the current study support or contradict the prevailing hypotheses on the comorbidity of severe mental disorders and SUDs?

Common factor models: Our findings do not appear to be at odds with common factor models, which postulate that common risk factors may increase the risk for both disorders. The earlier onset of BD among patients with excessive cannabis use may support the notion that common factors (such as genes, psychosocial stressors or personality traits) have increased the risk for both disorders. Furthermore, the high rate of lifetime use of illicit substances in patients compared to the general population may support a common factor model, in that the propensity to illicit substance use seems to be present even in BD individuals that have not developed excessive substance use.

Secondary substance use disorder models: Our findings do not seem to be in conflict with secondary SUD models, which propose that severe mental illness may cause SUDs. Rather, the finding that treatment delay was associated with subsequent excessive substance use supports the notion that excessive substance use may be an attempt to self-medicate symptoms or distress, i.e. that BD may cause excessive substance use.

Secondary psychiatric disorder models: Secondary psychiatric disorder models, in which substance abuse is suggested to cause or precipitate severe mental illness, are not contradicted by the present study's findings. The later onset in secondary BD and the earlier onset in individuals with preceding excessive cannabis use found in the current study, both support the notion that

excessive substance use may trigger BD even though this may seem incongruous. The higher AAO in secondary BD may be explained by a low constitutional vulnerability, and that a prolonged excessive substance use was necessary to elicit the BD in these individuals. The earlier onset in patients with excessive cannabis use prior to BD onset may be explained by either a high constitutional vulnerability interacting with cannabis use, or that cannabis is a substance with high potency for precipitating BD. The fact that our sample of excessive cannabis users had high rates of family history of affective/psychotic disorders supports the former hypothesis.

Bidirectional models: The findings of the present study contain little data to challenge or support the theory that excessive substance use increases the risk for BD and vice versa within individuals.

In conclusion, the findings of the present study appear to support the notion that the strong association between BD and excessive substance use may stem from many different mechanisms and relationships, i.e. that no single mechanism can explain all co-morbid cases. Such mechanisms may be that substance abuse precipitates BD, that patients self-medicate symptoms of BD with alcohol and drugs, and that common factors such as genes, elevated impulsivity or behavioral approach system sensitivity increase the risk for both disorders. More than one of the mechanisms may also operate within the same individual.

5.5 Clinical implications

The findings of the current study may have important implications for the treatment of BD patients. Because of the increased functional impairment and treatment non-compliance associated with excessive substance use, substance use should be targeted in treatment before the clinical signs of abuse or dependence have developed. In fact, due to the high rate of lifetime use of illicit substances among the patients and the possibility that *all* BD patients have an increased propensity for substance abuse, addressing substance use at an early point of the treatment is of great importance. Furthermore, individuals at high risk for developing BD should be warned about the possible precipitating effect of cannabis use.

The finding that the risk for onset of excessive substance use increases with increasing treatment delay implicates that early identification and treatment of BD is crucial. Thus, although the focus and knowledge on BD appears to be increasing, further education and information on BD for e.g. general practitioners and other primary health care providers may be needed. As much as 28% of the patients in the current sample had never received adequate pharmacological treatment. These were mainly patients with BD II or no history of psychosis. There are clear indications that even these patients benefit from such treatment (Grunze et al., 2004). Thus, effort

should be made to make pharmacological treatment more accessible even for BD patients without the most severe clinical presentations.

It should also be of considerable value for both the clinic and authorities involved in planning and reforming psychiatric treatment to know that excessive substance use does not appear to be an obstacle for initiation of pharmacological treatment of BD.

5.6 *Implications for future research*

This is a clinical study, and the following recommendations for future research will focus on clinical areas. However, the relationship between BD and excessive substance use also needs to be further investigated through research on biological mechanisms.

In the current study, different AAOs, as well as different directions for the association between treatment delay and excessive substance use, depending on the temporal relationship between the onsets of BD and excessive substance use were discovered. Thus, differentiating between primary and secondary BD appears to be necessary to discover important associations between substance use and several features of BD. There may also be differences in clinical characteristics between these groups. However, such an investigation was not part of the aims of the current study, but should be addressed in future research.

The complex relationship between AAO, type of substance used, sequencing and family history should be further explored in a greater sample allowing comparisons on several subgroup levels. Ideally, the sample should allow subdivision according to different degrees of familial loading in addition to the other subgroups suggested. Furthermore, in order to better clarify causal relationships regarding the impact of excessive substance use on the course and symptoms of BD and whether excessive substance use may precipitate BD, longitudinal and epidemiological studies are needed. Future research should also aim to clarify whether excessive substance use may trigger subsyndromal symptoms, affective episodes or the disease entity of BD.

Furthermore, increased knowledge of subjective experiences of substance use such as motives and perceived effects is needed to further evaluate secondary substance use models (such as self-medication hypotheses) and improve intervention strategies. The recently developed experience sampling methodology may be a worthwhile approach to such research, as it enables momentary and longitudinal assessment of individual experiences such as emotions, stress, substance craving and -use during daily life (Myin-Germeys et al., 2009).

Given the high risk for excessive substance use in BD, searching for potential resilience factors in BD subjects not developing excessive substance use could also be a worthwhile approach for future studies. Such knowledge would facilitate planning of preventive strategies.

6 CONCLUSIONS

The most important findings of the present study are that excessive substance use is associated with poorer functioning but not with more severe clinical characteristics, and that excessive cannabis use is associated with an earlier age at onset of bipolar disorder. Furthermore, patients with excessive substance use prior to the onset of bipolar disorder have a higher likelihood for short treatment delays compared to patients without, whereas long treatment delays are associated with an increased risk for subsequent excessive substance use.

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Appendix

Table 1. DSM-IV affective episode criteria.

<p>Major depressive episode:</p> <ul style="list-style-type: none"> - a period of at least 2 weeks with either depressed mood or loss of interest or pleasure in almost all activities - at least 3 (4 if only depressed mood or loss of interest) of the following symptoms must be present: <ul style="list-style-type: none"> • changes in appetite or weight • sleep or psychomotor activity • decreased energy • feelings of worthlessness or guilt • difficulty thinking, concentrating or making decisions • recurrent thoughts of death or suicidal ideation, plans or attempts - may involve psychotic symptoms in terms of delusions, hallucinations or thought disorders 	<p>Manic episode:</p> <ul style="list-style-type: none"> - a distinct period of at least 1 week (or less if hospitalization is required) with either abnormally and persistently elevated, expansive or irritable mood - at least 3 (4 if irritable mood only) of the following symptoms must be present: <ul style="list-style-type: none"> • inflated self-esteem or grandiosity • decreased need for sleep • pressure of speech • flight of ideas • distractibility • increased involvement in goal-directed activities or psychomotor agitation • excessive involvement in pleasurable activities with a high potential for painful consequences - the disturbance is not sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization - may involve psychotic symptoms in terms of delusions, hallucinations or thought disorders
<p>Hypomanic episode:</p> <ul style="list-style-type: none"> - a distinct period of at least 4 days with either abnormally and persistently elevated, expansive or irritable mood - the list of symptoms is identical to that of mania - the disturbance is not sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization - may not involve psychotic symptoms 	<p>Mixed episode:</p> <ul style="list-style-type: none"> - a period of at least 1 week in which the criteria are met both for a major depressive episode and a manic episode

Table 2. Lifetime substance use registration form.¹

Lifetime substance use: (fill inn) (0=never/occasionally, 1=monthly, 2=weekly, 3=daily)

	Lifetime	Onset	Duration		12-15	16-20	21-27	28-44	45-60	60+	i.v.
Alcohol - use											
Alcohol - intoxication											
Amphetamines ¹											
Cocaine ²											
Cannabis ³											
Ecstasy											
Heroin											
Other opiates ⁴											
Hallucinogenes ⁵											
Solvents ⁶											
Pharmacological agents ⁷											

¹ Incl. methamphetamine, khat and Ritalin, ² Incl. crack and coke leaves, ³ Incl. marihuana and hashish, ⁴ Incl. morphine, Methadone, Dolcontin, Ketogan, Petidin, Temgesic, Paralgin Forte etc. ⁵ Incl. LSD, mescaline, mushrooms, PCP etc. ⁶ Incl. lighter fluid, gasoline, glue etc. (for sniffing) ⁷ Incl. sedative (Vival, Rohypnol, Rivotril etc.) and pain-killing (Somadril) medication used without prescription or exceeding the prescription.

Instructions for completing the substance use section:

Lifetime: Tick if substance was ever used (at least one clear episode).

Onset: Age at first time substance was used.

Duration: Total number of years the substance was used. (Used once during one year=1 year)

Age interval: Within each age interval, a code is used to indicate how frequently the substance is used:

0 – no use or occasional use

1 – Monthly use

2 – Weekly use

3 – Daily use

i.v. : Tick if substance was used intravenously.

Alcohol:

Alcohol intoxication implies that the person drinks to get intoxicated or drunk.

Please note: Indicate whether the substance use has varied within each interval, especially if there have been periods with high consumption of alcohol (binge drinking) or a more regular consumption. Using the interviewees own word is suggested.

Notes:

¹ This instrument was translated to English for the purpose of presentation in this thesis and is not an official translation.

RESEARCH ARTICLE

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Excessive substance use in bipolar disorder is associated with impaired functioning rather than clinical characteristics, a descriptive study

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Abstract

Background: There is a strong association between bipolar disorder (BD) and substance use disorder (SUD). The clinical and functional correlates of SUD in BD are still unclear and little is known about the role of excessive substance use that does not meet SUD criteria. Thus, the aims of the current study were to investigate lifetime rates of illicit substance use in BD relative to the normal population and if there are differences in clinical and functional features between BD patients with and without excessive substance use.

Methods: 125 consecutively recruited BD in- and outpatients from the Oslo University Hospitals and 327 persons randomly drawn from the population in Oslo, Norway participated. Clinical and functional variables were assessed. Excessive substance use was defined as DSM-IV SUD and/or excessive use according to predefined criteria.

Results: The rate of lifetime illicit substance use was significantly higher among patients compared to the reference population (OR = 3.03, CI = 1.9-4.8, $p < .001$). Patients with excessive substance use (45% of total) had poorer educational level, occupational status, GAF-scores and medication compliance, with a trend towards higher suicidality rates, compared to patients without. There were no significant group differences in current symptom levels or disease course between groups.

Conclusion: The percentage of patients with BD that had tried illicit substances was significantly higher than in the normal population. BD patients with excessive substance use clearly had impaired functioning, but not a worse course of illness compared to patients without excessive substance use. An assessment of substance use beyond SUD criteria in BD is clinically relevant.

Background

Comorbid bipolar disorder (BD) and substance use disorder (SUD) have been found to be highly prevalent in both epidemiological and clinical studies, with rates of SUD in subjects with BD ranging from 35-60% [1-6]. The high prevalence is found across different age groups and also in first episode BD samples [7,8].

So far, most studies in BD have investigated only substance use fulfilling SUD criteria. Investigating a broader range of substance use in BD could be relevant because people with severe mental disorders are more likely to experience negative consequences from using relatively

small amounts of psychoactive substances [9]. Moderate alcohol consumption in BD is associated with more severe manic symptoms compared to abstinence, and to poorer social and familial adjustment and increased health-care use [10]. To the best of our knowledge, only one study assessed substance use in BD more globally, reporting that 46% had SUDs and 8% had SUD-sub-threshold substance use. In addition, the authors indicated that another substantial proportion used illicit substances occasionally [11].

Clarifying whether there is an increased use of substances in BD may increase our understanding of the psychopathology underlying the increased risk of abuse or dependence. Although most studies show a large prevalence of BD and SUD comorbidity, the rates vary

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widely. This variation could be mirroring differences in substance use in the general population where the BD sample is recruited. In a smaller sample from an earlier part of our ongoing study, we showed elevated rates of lifetime use of illicit substances among patients with psychotic disorders (including BD) compared to the general population [12], and differences in patterns of substance use between schizophrenia and BD [13]. Due to the small number of patients with BD included in our earlier report, a separate comparison of BD patients with the general population sample was not implementable. Thus, there is a need for studies comparing BD subjects with reference populations on substance use and they should be done with samples from the same geographical area within the same time period.

In the current literature, BD with comorbid SUD is consistently referred to as associated with a poorer disease course and with reduced functioning compared to BD without SUD. The findings regarding the effects of SUD on BD are however divergent. To explore this more thoroughly we did a search in PubMed (terms bipolar disorder, substance abuse and outcome), and in addition tracked all cited references in key publications (Additional file 1). The main finding from this search was that the only consistently reported findings were delayed recovery and lower remission rates [14-22] as well as faster relapses [14,23-25] in groups of BD patients with SUD (both lifetime/current substance - and/or alcohol use disorders) compared to BD without SUD. Furthermore, there appears to be extensive evidence for elevated suicidality rates in BD with SUD compared to BD without [18,20,26-37], although several studies also report no significant differences [19,38-42]. Medication compliance rates are also relatively consistently reported to be lower in BD with SUD compared to BD without [18,19,29,43-46] although a few studies report lack of differences [38,42]. Another consistent finding is that the prevalence of psychotic symptoms does *not* appear to be elevated among BD patients with SUD compared to patients without [18,19,28,38,47,48], and there is neither a tendency towards increased numbers of affective episodes [19,27,31,48,49].

The findings are more divergent regarding rapid cycling: as some studies did [38,40,50-52] and some did not [19,29,53] find this to be more prevalent in the SUD patients. The same inconsistency is found for the prevalence of mixed episodes, some studies found this phenomenon to be more common [14,18,39,50,54] while others did not [17,47,55] in the SUD patients. There are also inconsistencies regarding age of onset for BD; here some report earlier onset for patients with SUD [26,29-31,50,51,56,57] while others do not find any differences compared to BD patients without SUD [18,19,38,47,55,58]. Studies also diverge as to whether

affective symptoms are of increased severity in BD patients with SUD compared to BD patients without [18,21,26,39,42,47,49,50,59,60]. Furthermore, the number of hospitalizations or days in hospital is found to be elevated in BD patients with SUD in some studies [29,31,50,55,61-64] as opposed to in others [18,26-28,38,48,56,65].

Findings concerning other functional variables such as decreased global functioning [19,26,38,39,47,48,56,60,66], social functioning [20,21,27,29,38,58,60,67], educational level [19,20,26,31,38,50,56,60], and quality of life [20,21,26,58,60,61] in BD with SUD also diverge. Finally, some studies find lower employment status in BD with SUD compared to BD without [21,24,29,67] while others do not [28,43,50,56], and two studies even find better employment rates in BD with SUD [19,61]. The current evidence therefore suggests that BD with comorbid SUD is clearly associated with worsening of *some* clinical and functional characteristics: Length of affective episodes and relapse rates, risks of suicidality and compliance to medication. However, substance abuse does not appear to be as consistently associated with a more severe course and outcome as frequently indicated in the literature.

In the present study, we aim at investigating differences in relevant outcome variables in a sample of BD patients with and without substance use. The present paper is based on a cross-sectional study of consecutively referred patients with BD from a catchment-area based psychiatric service, and a population survey of the use of illicit substances in the same area within the same time period. Our aims were to answer the following questions:

- 1) Is the rate of lifetime use of illicit substances higher in the patient sample than in the reference population?
- 2) Do patients with and without excessive substance use, defined as SUD and/or excessive use, differ on clinical and functional characteristics, in terms of disease course variables, current symptom levels and functioning?

Methods

Participants

125 patients with DSM-IV bipolar disorder (BD I $n = 71$ and BD II $n = 54$), participated in the study. The sample is part of an ongoing study of schizophrenia and bipolar disorder (the Thematically Organized Psychosis Research - TOP study). The BD patients were consecutively recruited between 2003 and 2007 from the psychiatric units (in- and outpatient) of the three major hospitals in Oslo. The exclusion criteria for all participants were: history of moderate/severe head injury, neurological disorder, mental retardation, age outside the range of 18-65 years, and not speaking a Scandinavian

language. All participants gave informed consent, and the project was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

A sample from the general population was used as a reference group for rates of lifetime use of illicit substances, collected by the Norwegian Institute for Alcohol and Drug Research (SIRUS). SIRUS regularly conducts surveys of the Norwegian population's consumption of illicit substances by personal interviews via standardized questionnaires. Subjects are randomly selected according to a detailed selection protocol and weighted to age, gender and address [68]. For the purpose of this study, we used a reference group of 327 subjects from 2004 SIRUS data for Oslo, with participants aged 18-65. There was no age difference between the patient group and the reference group (35.6, SD 11.7 vs. 36.0, SD 12.0), but the proportion of women was significantly greater in the patient sample (64.8% vs. 51.4%, $X^2 = 6.59$, $df = 1$, $p = 0.010$).

Clinical assessment

Clinical assessment was carried out by trained clinical psychologists and psychiatrists. Diagnoses were established using the Structured Clinical Interview for DSM-IV, modules A-E [69]. General non-psychotic symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) [70], depressive symptoms with the IDS-C [71], (hypo)manic symptoms with the Young Mania Rating Scale (YMRS) [72] and current functioning by the Global Assessment of Functioning Scale (GAF) [73], split version [74]. The Medication Adherence Rating Scale (MARS) [75] was used to measure compliance to medication. A total of 103 patients (82.4%) completed the MARS. Eight patients (6.4%) did not complete because they were not using any medication at the time of the evaluation. Among the patients not completing the MARS, there was no significant difference in the proportion with or without excessive substance use.

All interviewers were trained based on the training program at UCLA (CA, USA) and participated in regular diagnostic consensus meetings. A good inter-rater reliability was achieved with an overall kappa score of 0.77 (95% CI: 0.60-0.94). The reliability for symptom assessments was also good, with an intraclass correlation coefficient (1.1) of 0.71 for the PANSS general subscale, and of 0.86 for both symptom and function GAF scores (for details, see Ringen et al. 2007b).

Some of the variables frequently reported in the literature, like prevalence of mixed episodes and rapid cycling, were not investigated in the present study, due to a study design that did not focus on specific characteristics of the affective episodes. Disease course was assessed by means of SCID criteria, which lack the specificity needed for satisfactory reliability of such phenomena.

Substance use assessments and excessive substance use definitions

Patients were asked for age at first experience with drinking alcohol and using non-alcoholic drugs (including non-prescribed anxiolytic and hypnotic medicines). Lifetime use of all substances through age intervals (age 12-15, 16-20, 21-27, 28-44, 45-60, 60+) was registered separately in categories of daily, weekly, monthly or occasional/no use within each interval, based on the possibility of different use patterns and of differences in the pathophysiological influence of substances across different age periods. Predominantly *daily* use of alcohol and predominantly *weekly* use of a non-alcoholic substance throughout an age interval across a minimum of 4 years were considered *excessive*, and substance use according to these definitions is subsequently termed *excessive use*. Structured interviews about substance use during the past 6 months were performed. Alcohol use was assessed by number of units and non-alcoholic substance use by number of incidents. Different non-alcoholic substances were asked for specifically and the use was quantified by totaling the number of incidents recalled. Urine samples were also collected and corresponded well with patients' own reports of consumption of non-alcoholic substances in previous weeks [13]. There were no statistically significant differences among the levels of substance use (number of units of alcohol or number of incidences of use of non-alcoholic substances) the last 6 months between patients fulfilling SUD criteria and patients with excessive use. But these two groups combined differed significantly from the patients with neither SUD nor excessive substance use. Thus, for the subsequent analyses, patients with SUD and patients with excessive use were aggregated in an "*excessive substance use group*". Patients with none of these are subsequently named "*no use group*".

The mean age was 34.8 (SD 11.8) in the excessive substance use group and 36.2 (SD 11.2) in the no use group (n.s.). In the excessive substance use group, 54% were female, which was significantly different from the no use group, where 74% were female ($X^2 = 5.608$, $p = 0.018$). 93% were Caucasian in the excessive substance use group, and 90% in the no use group (n.s.). Median duration of illness was 9.5 years (IQR 12) in the excessive substance use group and 11.5 years (IQR 16.75) in the no use group (n.s.).

Statistical procedure

All analyses were done using the Statistical Package for the Social Sciences (SPSS) version 16.0. The limit for significance was set to 0.05 (two-sided). Chi-square tests and Fisher's exact tests were used when investigating group differences on categorical data. Group differences in independent samples were explored with Student's t-tests and ANOVAs on normally distributed continuous variables and Mann Whitney U-tests and Kruskal

Wallis tests for variables with a skewed distribution. The distribution of skewed variables is presented through medians and interquartile ranges (IQR). Binary logistic regression analysis was used for calculating odds ratios, controlling for relevant variables. Correlations between group membership, outcome measures and background variables that might mediate their relationships were explored through Pearson and Spearman rank correlations. The presence of possible confounder variables was explored through hierarchical multiple regression analysis. The Kaplan-Meier Survival Analysis was used to compare time in remission across the two groups.

For the analyses related to research question 2, the levels of relevant demographic and clinical measures were compared for the excessive substance use group versus the no use group. Since the distribution of sex was significantly different in the excessive substance use group and the no use group, it was considered a potential confounder in the associations between group membership and outcome variables and possible mediating effects were investigated.

Results

The prevalence of lifetime use of illicit substances was 65% in the patient sample and 40% in the general population sample. When corrected for age and sex, the risk of lifetime use of illicit substances was significantly and three times greater in the patient sample compared to the reference population (OR = 3.03, CI = 1.9-4.8, $p < .001$).

The prevalence of SUDs and excessive substance use are presented in Table 1.

Regarding clinical and functional outcome variables (Table 2), we found that the no use group had significantly more years of education than the patients with excessive substance use (15.1, SD 2.9 versus 13.5, SD 2.6, $p = 0.001$). The proportion that was employed/full time students was significantly smaller in the excessive substance use group

(21% versus 45%, $p = 0.006$). We also found that the excessive substance use group had significantly lower mean GAF S and F scores than the no use group (52.9, SD 10.7 versus 59.7, SD 11.1, $p = 0.001$ and 50.3, SD 11.3 versus 57.2, SD 12.1, $p = 0.002$, respectively). Correlation analyses revealed that number of years of education correlated with the excessive substance use group (Pearson's $r = -0.29$, $p = 0.001$), and GAF S and F scores (GAF S: Pearson's $r = 0.22$, $p = 0.016$, GAF F: Pearson's $r = 0.21$, $p = 0.018$). After correction for number of years of education, age and sex, there was still a significant association between excessive substance use and lower GAF S score (group membership entered as last variable, $\beta = -0.24$, $p = 0.009$), and lower GAF F score ($\beta = -0.20$, $p = 0.034$). Furthermore, the excessive substance use group had a significantly higher median MARS score, i.e. was less compliant by self-report than the no use group (8, IQR 5 versus 7, IQR 3, $p = 0.010$). There was also a strong trend that the excessive substance use group had more suicide attempts than the no use group ($p = 0.053$).

We found no significant differences in affective and general symptomatology as measured by the IDS-score, YMRS-score or PANSS general score between the patients with and without excessive substance use (Table 2). The proportion of patients in remission was not significantly different across the two groups, nor was time in remission. No significant differences were found between the groups in age at onset of BD, number of elevated episodes (manic/hypomanic), number of depressive episodes, or bipolar subtype distribution (BD I vs. BD II). No significant differences between the groups were found in lifetime prevalence of psychotic symptoms. Regarding the latter, a separate analysis comparing patients that only excessively used psychoactive substances known to induce psychotic symptoms (cannabis and centrally stimulating agents) with the no use group revealed no significant differences ($X^2 = 0.059$, $p = 0.564$). No significant differences were found regarding lifetime hospital admission or total number of admissions. Among the ones admitted, there was a trend that the duration of admissions was shorter in the excessive substance use group ($p = 0.056$). These analyses were repeated for only patients fulfilling SUD criteria versus the no use group (excessive use patients excluded), revealing no additional significant differences between the two groups. To investigate whether alcoholic and non-alcoholic substances influenced outcome in different directions, the alcoholic and non-alcoholic excessive substance use groups were compared with the no use group separately. This yielded no new significant associations.

Discussion

The main findings of the present study are that patients with BD had a significant increase (OR of 3) of lifetime

Table 1 Prevalence of lifetime substance use disorders and of excessive use in patient sample, N (%)

	N = 125
SUD total	38 (30.4)
Alcohol use disorder	26 (20.8)
Cannabis use disorder	15 (12.0)
Other non-alc. substance use disorder	14 (11.0)
Excessive use total	18 (14.4)
Excessive alcohol use	7 (5.6)
Excessive cannabis use	13 (10.4)
Excessive use other non-alc. substances	2 (1.6)
SUD + excessive use	56 (44.8)

SUD and excessive substance use are here mutually exclusive categories. Within these categories, some patients meet the criteria for two or more substance use disorders or can excessively use two or more substances.

Table 2 Clinical course and functional outcome variables in the “excessive substance use” group versus the “no use” groups

	Excessive substance use group, N = 56	No use group, N = 69	Test statistics/p-value	Effect sizes
IDS-C, median (IQR)	16.5 (17)	13.5 (20)	U = 1640.5, p = 0.853 ^a	
YMRS, median (IQR)	2 (3)	2 (5)	U = 1730.5, p = 0.393 ^a	
PANSS general, mean (SD)	26.1 (5.9)	24.6 (6.0)	t = -1.384, df = 122, p = 0.169 ^d	
Age at onset of BD (years), median (IQR)	20 (9)	19 (10)	U = 1894.0, p = 0.962 ^a	
Duration of illness, median (IQR)	9.5 (12)	11.5 (16.75)	U = 1739.0, p = 0.407 ^a	
In remission, n (%)	19 (35)	31 (46)	X ² = 1.515, p = 0.218 ^b	
Time in remission, months, median (IQR)	3 (4)	5 (7.25)	X ² = 2.511, p = 0.113 ^c	
No. of elevated mood episodes, median (IQR)	3 (8.5)	2 (4)	U = 1619.0, p = 0.288 ^a	
No. of depressive episodes, median (IQR)	4 (9)	3 (8)	U = 1716.0, p = 0.604 ^a	
Bipolar disorder type, BD I, n (%)	30 (54)	41 (59)	X ² = 0.431, p = 0.512 ^b	
Psychosis, n (%)	20 (36)	32 (48)	X ² = 1.604, p = 0.205 ^b	
No. of suicide attempts, median (IQR)	0 (1)	0 (1)	U = 600.0, p = 0.053 ^a	
Hospitalized (lifetime), n (%)	35 (65)	45 (67)	X ² = 0.074, p = 0.786 ^b	
No. of admissions, median (IQR)	1 (2.8)	1 (3)	U = 1814.0, p = 0.745 ^a	
Duration of admissions (months), median (IQR)	1.5 (4.2)	3.3 (5)	U = 568.0, p = 0.056 ^a	
MARS score, median (IQR)	8 (5)	7 (3)	U = 915.5, p = 0.010 ^a	Diff. in mean rank = 15.17
Years of education, mean (SD)	13.5 (2.6)	15.1 (2.9)	t = 3.307, df = 123, p = 0.001 ^d	Cohen's d = 0.596
Currently employed/full time students, n (%)	12 (21)	31 (45)	X ² = 7.564, p = 0.006 ^b	Phi = -0.246
Marital status (married/living as married), n (%)	20 (36)	26 (38)	X ² = 0.051, p = 0.821	
GAF S, mean (SD)	52.9 (10.7)	59.7 (11.1)	t = 3.458, df = 123, p = 0.001 ^d	Cohen's d = 0.624
GAF F, mean (SD)	50.3 (11.3)	57.2 (12.1)	t = 3.112, df = 123, p = 0.002 ^d	Cohen's d = 0.561

IQR = interquartile range. ^aMann Whitney U-test, ^bChi-square test, ^cLog rank (Mantel Cox) test, ^dStudent's t-test.

use of illicit substances compared to the general population, and that excessive substance use was associated with poorer functioning but not with worse illness course characteristics or current symptom levels.

To the best of our knowledge, this is the first study to report lifetime illicit substance use in a clinical sample of BD patients compared to the reference population. Our data indicate that the risk is greater than in the general population not only to develop SUDs, but also to use such drugs at a SUD-subthreshold level. Despite large research efforts, the mechanisms involved in the increased substance use in BD are not known. Several studies have found increased impulsivity and novelty seeking in BD patients [76,77], which have also been linked to substance use [78,79]. This could partially explain the increased tendency to experiment with and excessively use substances among subjects with BD [80]. The same could be true for Behavioral Approach System (BAS) dysregulation, in which high BAS sensitivity has been linked to both increased risk of (hypo)manic episodes [81] and substance abuse [82]. Searching for potential protecting factors in BD subjects not developing SUD could be a worthwhile approach for future studies.

The total alcohol use disorder rate of 21% found in the present study was in the lower range of earlier

clinical reports on samples consisting of both BD I and II disorders [20,30,83], and the higher SUD rates in males compared to females is in accordance with earlier findings [57,58]. Thus, the somewhat higher proportion of females in our sample could explain the lower alcohol use disorder rate. Furthermore, both drug use and alcohol use patterns differ between countries and cultures. The average alcohol intake in Norway is significantly lower than the European continent, the UK and the US [84,85], which could also explain the lower risk of alcohol use disorder in the patient group in the present study.

There were several indicators of a poorer functioning in the excessive substance use group compared to the no use group, including length of education and employment rate. The hierarchical multiple regression analyses also indicated direct associations between excessive substance use and lower GAF scores that were not mediated by years of education. Although earlier studies are inconsistent, our findings of poorer functioning in the excessive substance use group are in line with several studies showing greater functional impairment associated with comorbid SUD [20,21,29,60]. The excessive substance use group also had poorer compliance, which is in accordance with earlier research [45,46]. The trend towards shorter hospital admissions found in the

excessive substance use group could also be interpreted as reduced compliance, as shorter admissions may be an expression of treatment non-compliance. Alternatively, inpatient treatment facilities are not optimal for treating BD patients with excessive substance use which may lead to shorter inpatient treatment. Shorter durations of psychiatric hospital admissions among patients with comorbid mental illness and SUD have also been found in earlier studies [86].

We did not find evidence that the presence of excessive substance use was associated with more severe BD specific disease characteristics. Earlier studies mainly investigated DSM-IV SUD, which is more narrowly defined than the present study's excessive substance use category. However, when we analyzed the narrowly defined SUD group, we did not find different results compared to the excessive substance use group. Furthermore, we found that the substance use levels among patients with excessive use were similar to patients with SUDs. Comparing our results with studies investigating SUD should therefore be relevant. The present lack of association between excessive substance use and current affective symptomatology is in line with several other studies finding no differences across groups defined by SUD in these variables [18,50]. It has also been hypothesized that SUD may trigger BD in individuals without a great constitutional vulnerability for the disorder [48,87]. Thus, a lack of worsening of BD illness characteristics in the presence of SUD may be explained by a lower vulnerability. Our finding of no relationship between excessive substance use and an earlier onset of the BD is consistent with some studies [55] but in contrast to others [29], and these discrepancies are difficult to explain. The present lack of significant differences in remission variables was unexpected, since prolonged affective episodes are found quite consistently by earlier research [20]. However, there were numerical differences between the groups in the expected direction on these variables, so this difference could reach statistical significance in a larger sample. Furthermore, the present finding of no relationship between excessive substance use and number of affective episodes is in line with previous research [49] although this is sparsely investigated. Finally, the similar distribution of bipolar subtypes across the groups in our study converges with some studies [20,83], but is contrary to those finding higher SUD rates in bipolar I disorder compared to bipolar II disorder [1,6]. Our findings of no differences in BD illness severity between patients with or without excessive substance use is in accordance with a recent study on BD I disorder with or without SUD on several proxies for BD severity [27].

The trend towards increased suicidality rates as well as the lower GAF S scores found in the excessive substance

use group in the present study, could be signs of a poorer general psychiatric outcome not linked to a more severe BD. Increased suicidality is seen in a number of psychiatric disorders and has been found associated with SUD alone [88], and with the combination of SUD and a variety of psychiatric disorders [89-91]. Thus it appears reasonable to link the increased suicidality more to the excessive substance use per se than to a more severe BD course. The lower GAF S scores in our excessive substance use group were not reflected in increased symptoms as measured by the IDS and the YMRS as could be expected, and may also be directly related to the substance use itself or to the burden of having two disorders. In summary, excessive substance use does not appear to be related to more severe specific BD illness characteristics, but to a more severe general psychiatric outcome in terms of worse global clinical features unspecific to psychiatric diagnosis and frequently seen in association with substance abuse alone.

Our finding concerning psychosis is in accordance with previous studies reporting a lack of association between SUD and higher lifetime rates of psychosis in BD [18]. This is not surprising given that these studies did not specifically investigate the use of cannabis and centrally stimulating agents known to induce psychotic symptoms during intoxication [92,93] and increase the risk of psychotic disorders [94,95]. The lack of association between psychosis and excessive use of these psychosis inducing substances found in the present study is somewhat surprising, but could be related to a high psychosis frequency in general in BD patients, thereby reducing the relative effect of substance use.

The present study's approach of adding patients with a SUD-subthreshold excessive substance use to the SUD group has additional value, in that we demonstrate that SUD criteria are not necessarily the appropriate cut-off when addressing and assessing harmful substance use in BD. Our findings may also have important implications for treatment of BD patients with excessive substance use. Because of the increased functional impairment and treatment non-compliance associated with excessive substance use, substance use should be targeted in treatment before the clinical signs of abuse or dependence have developed. Our findings further demonstrate that patients with a considerable amount and frequency of substance use may not necessarily fulfill SUD diagnostic criteria.

The inconsistency revealed in the literature regarding differences in clinical and functional characteristics between BD with and without SUD is somewhat unexpected, as several papers including reviews of the topic generally state that there is consistent evidence that a comorbid SUD is associated with more severe features.

This is a relatively new field, thus citation and publication biases may be a problem. Studies also vary to a great extent in operationalizations and methodology, which may explain some of the discrepancies. Furthermore, studies setting out to answer questions about the associations between comorbid SUD and outcome in BD patients are few compared to studies that focus on other issues and report relationships between comorbid SUD and outcome as secondary findings. Also, since only a few studies display effect sizes in addition to significance levels, little is known about the strength of the associations. Thus, there is a great need for more well-designed and hypothesis-driven studies addressing this question as well as future efforts to agree on methodology.

The present study has some limitations. The sample in the present study was too small to investigate current use levels or non-alcoholic substance types separately. Furthermore, since this is a cross-sectional study, no conclusions of causality may be drawn regarding the association between excessive substance use and the functional level. Thus, whether these relationships are due to negative effects from the excessive substance use, or related socioeconomic factors, cannot be determined. Also, the sample size is relatively small, with an increased risk for type II errors. However, there are few substantial numerical differences between the groups, thus an increase in sample size would not lead to additional significant differences. This is a well characterized catchment area study, covering both in- and outpatient units including substance abuse clinics.

Conclusions

The current findings show that there is a significant increase in illicit substance use in BD compared to general population with an OR of 3. Patients with excessive substance use have indications of impaired functioning and some signs of a more severe general psychiatric outcome, but not worse illness course characteristics or current symptom levels. This has implications for current treatment and should lead to more research into the underlying psychopathological mechanisms.

Additional file 1: Additional file 1 provides an overview table of the literature reported in the background section concerning the effect of substance use disorders on BD. The table is organized in two parts; Part I: "Reported effects of substance use disorders on measures of functioning and general psychopathology", and Part II: "Reported effects of substance use disorders on measures of illness course and clinical characteristics specific to bipolar disorder". Some of the reviewed studies appear in both Part I and Part II.
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Acknowledgements

The study is part of the TOP study group and was funded by grants from the South-Eastern Norway Health Authority (123/2004; 258/2006; 069/2007) and from the Research Council of Norway (167153/V50; 164778/V50). The funding source had no involvement in the authors' work. The authors thank the other members of the TOP Study group and the patients that participated in the study. We further thank the Norwegian Institute for Alcohol and Drug Research for kind permission to use their database on illicit drug use in Oslo.

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Authors' contributions

TVL participated in planning of the current study, the collection of data, did the statistical analyses and wrote the first draft of the paper and coordinated the writing process. OAA, KS and IM participated in planning of the study, supervised the data collection and statistical analyses. PAR, AOB, SL and IA participated in the data collection. All authors have made substantial contributions to writing of the manuscript and have approved the final version.

Competing interests

The authors declare that they have no competing interests.

Received: 7 August 2009

Accepted: 27 January 2010 Published: 27 January 2010

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Pre-publication history

The pre-publication history for this paper can be accessed here:<http://www.biomedcentral.com/1471-244X/10/9/prepub>

doi:10.1186/1471-244X-10-9

Cite this article as: Lagerberg et al: Excessive substance use in bipolar disorder is associated with impaired functioning rather than clinical characteristics, a descriptive study. *BMC Psychiatry* 2010 **10**:9.

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Additional file 1.

Part I: Reported effects of substance use disorders on measures of functioning and general psychopathology.

Publication	Study	Methods and sample characteristics	Type and measure of SUD	Type of functional outcome and general psychopathology							
				Educational level	Employment status	Social functioning	Quality of life	Medication compliance	Global functioning	Suicidality	Hospitalization
Reich & Himmelhoch, 1974	Lithium Clinic, Yale-New Haven Hospital, USA	N=65, BD I	Excessive alcohol use								Increased (level of significance not presented)
Morrison et al., 1974	VA Hospital, San Diego, California, USA	N=38, BD I	Alcoholism	No effect						Increased (level of significance not presented)	Increased (level of significance not presented)
Winokur et al., 1995	NIMH Collaborative Study on the psychobiology of depression, USA	N=231, BD I-II and schizoaffective disorder, 5 year prospective	AUD						No effect	Increased in females only	No effect
Tohen et al., 1990	McLean Hospital, Massachusetts, USA.	N=75, BD I, 4 year prospective	Alcoholism		Reduced, OR=8.2 (1.2-55.7)						
Brady et al., 1991	VA Medical Center, Charleston, South Carolina, USA	N=20 (total N=100), BD I inpatients, 97% males	SUD								Increased (level of significance not presented)
O'Connell et al., 1991	St. Vincent's Hosp. and medical center, New York, USA	N=248, BD I-II, 1 year prospective	SUD						Reduced		
Sonne et al. 1994	Medical U. of South Carolina, USA	N=44, BD I-II, in- and outpatients	SUD current/lifetime	Reduced	No effect						Increased in current SUD only
Tsai et al., 1997	Taiwan (Chinese patients)	N=158 BD I-II	AUD	No effect		No effect		No effect	No effect	No effect	No effect
Bauer et al., 1997	Providence VA medical center, Rhode Island, USA	N=103, BD I-II	SUD								No effect
Keck et al., 1998	U. of Cincinnati Hospital, USA.	N=134, BD I, inpatients, 1 year prospective	SUD		No effect			Reduced			
Pini et al., 1999	Pisa Center, Italy	N=125, psychotic BD, inpatients	SUD	No effect	No effect				No effect		No effect

Weiss et al., 2005	STEP-BD, USA	N=1000, BD I+II	SUD current, lifetime SUD	Reduced in current SUD only		Reduced	Reduced		Increased	
Goldstein et al., 2005	NIMHS "COBY", USA	N=446, BD I+II and NOS, children and adolescents	SUD						Increased OR=2.76 (1.21-6.28)	
Goldstein et al., 2008	NIMHS "COBY", USA	N=249, BD I+II and NOS, adolescents	SUD					No effect	Increased OR=2.8 (1.3-6.2)	
Haro et al., 2006	EMBLEM, 14 European countries	N=3536, BD I	SUD		Reduced	No effect		Reduced	Increased	Increased
Van Rossum et al., 2008	EMBLEM, 14 European countries	N=3425, BD I, 12 weeks prospective	SUD		Reduced OR=2.47 (1.44-4.26)	No effect	Reduced			
Manwani et al., 2007	McLean Hospital, (several treatment programs), Massachusetts, USA	N=115, BD I+II, inpatients, outpatients	SUD				Reduced			
Baldessarini et al., 2008	Adelphi Bipolar Disorders Disease-Specific Program, UK and USA	N=429, BD I+II and NOS	AUD				Reduced RR=2.26			
Goldstein and Levitt, 2008	NESARC, USA	N=1411, BD I	SUD			No effect (reduced "role emotional" in females)				No effect
Cardoso et al., 2008	Hospital de Clinicas de Porto Alegre, Brazil	N=186, BD I+II	AUD	Reduced			No effect	Reduced	Increased	No effect
Sentissi et al., 2008	INSERM, Paris, France	N=73, BD I+II	SUD			No effect	No effect			
Khalsa et al., 2008	McLean/Harvard First Episode project, Massachusetts, USA.	N=216, BD I	SUD						No effect	
Baca-Garcia et al., 2009	NYSPI and Columbia U., New York, USA	N=97, BD	AUD					No effect	No effect	
Sajatovic et al., 2009	Case Western Reserve U. School of Medicine, Ohio, USA	N=113, BD I	ASI-score					Reduced		
Hoblyn et al., 2009	Veterans Affairs adm. database, California, USA	N=2963, BD I, II, NOS	SUD							Increased for all substances, RR=2.49-3.58 (2.02-5.03)

Mazza et al., 2009	Catholic U. of sacred heart, Rome, Italy	N=131, BDI-II, cycloth., 1 year prospective	SUD	No effect		Reduced	No effect		No effect		
Sublette et al., 2009	NYSPI, New York and WPIC, Pittsburgh, USA	N=138, BDI-II	AUD, SUD							Increased in BD I, OR=2.54 (0.78-8.23)(alc.), OR=4.70 (1.20-18.32) (drugs) and reduced in BD II, OR=0.71 (0.19-2.76 (alc.), OR=0.58 (0.15-2.24) (drugs)	
Neves et al., 2009	U. Federal de Minas Gerais, Brazil	N=239, BDI-II, In- and outpatients.	Alcoholism, drug addiction							No effect (increased in bivariate but not multivariate analyses	

Abbreviations: U. = university, SUD = substance use disorder, AUD = alcohol use disorder, OR = odds ratio, RR = risk ratio, HR = hazard ratio.
When no specification on type of BD, in/outpatient status etc. is listed, no information was presented in the paper. Substance use disorder is “lifetime” when no information on whether it is current or lifetime is listed. The studies are presented chronologically, except when all or parts of participants are shared between studies. In this case, the studies are grouped together. Effect sizes (OR, RR and HR) are listed with 95% CI in parentheses if these are reported in the study.

Part II: Reported effects of substance use disorders on measures of illness course and clinical characteristics specific to bipolar disorder.

Publication	Study	Methods and sample characteristics	Type and measure of SUD	Illness Course and Clinical Characteristics Bipolar Disorder							
				Early AAO of BD	Recovery	Relapse	No. of affective episodes	Severity of symptoms	Mixed episodes	Psychosis	Rapid cycling
Morrison et al., 1974	VA Hospital, San Diego, California, USA	N=38, BD I	Alcoholism	Increased			No effect				
Himmelhoch et al., 1976	Affective Disorder Clinic, Yale U. Medical Center, USA	N=84, manic-depressive outpatients, 5 year prospective	Alcohol and drug abuse		Reduced (increased risk of "poor response" as defined as either lack of remission or relapse during follow-up)				Increased		
Keller et al., 1986	NIMH Collaborative Study on the psychobiology of depression, USA	N=155, BD I, 18 month prospective	AUD		Reduced (sign. level not presented)				Increased (sign. level not presented)		
Winokur et al., 1995	NIMH Collaborative Study on the psychobiology of depression, USA	N=231, BD I+II and schizoaffective disorder, 5 year prospective	AUD		No effect	No effect	No effect			No effect	
Coryell et al., 1998	NIMH Collaborative Study on the psychobiology of depression, USA	N=113, 15 year prospective	Alcoholism		Reduced						
Tohen et al., 1990	McLean/Harvard First Episode project, Massachusetts, USA.	N=24, BD I, 4 year prospective	Alcoholism			Increased HR=13.9 (1.4-138.0)					
Tohen et al., 1990	McLean Hospital, Massachusetts, USA.	N=75 BD I, 4 year prospective	Alcoholism			Increased HR=8.9 (1.2-12.6)					
Tohen et al., 1996	McLean/Harvard First Episode project, Massachusetts, USA.	N=123, BD I, 2 year prospective	Current SUD		Reduced				No effect		
Sonne et al. 1994	Medical U. of South Carolina, USA	N=44, BD I+II, in- and outpatients	SUD current/lifetime	Increased				No effect	Increased (dysphoric mania)		Increased (mood-swings, sign. level not presented)
Tsai et al., 1997	Taiwan (Chinese patients)	N=158 BD I+II	AUD	No effect						No effect (in first episode)	Increased

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Perlis et al., 2006	STEP-BD, USA	N=1469, BD I+II, 2 years prospective	SUD current, lifetime	No effect	Reduced	Increased for mania with current SUD, HR=1.61 (1.01-2.57)						
Verduin et al., 2005	VA Cooperative Study, 11 sites in USA	N=328, inpatients, veterans, public sector	SUD	No effect	Reduced	No effect (prior year)	No effect (current psychosis)	No effect	No effect	No effect	No effect	No effect
McKown et al., 2005	UCLA Mood Disorders Research Program, USA	N=30, BD I+II	AUD									Increased (with high no. of drinks per day)
Goldstein et al., 2008	NIMHS "COBY", USA	N=249, BD I+II, NOS, adolescents	SUD	No effect	No effect		No effect	No effect	No effect	No effect	No effect	No effect
Haro et al., 2006	EMBLEM, 14 European countries	N=3536, BD I	SUD	Increased								No effect
Van Rossum et al., 2008	EMBLEM, 14 European countries	N=3425, BD I, 12 weeks prospective	SUD		Reduced		Increased for mania, not depression	Increased for mania, not depression				
Goldstein and Levitt, 2008	NESARC, USA	N=1411, BD I	SUD			No effect (12 month prevalence)	Increased in females only					
Cardoso et al., 2008	Hospital de Clinicas de Porto Alegre, Brazil	N=186, BD I+II	AUD	Increased			Increased for depression, not mania	Increased for depression, not mania			Increased (in first episode)	
Sentissi et al., 2008	INSERM, Paris, France	N=73, BD I+II	SUD	No effect								
Baca-Garcia et al., 2009	NYS Psychiatric Institute and Columbia U., New York, USA	N=97, BD	AUD				No effect	No effect				
Mazza et al., 2009	Catholic U. of sacred heart, Rome, Italy	N=131, BD I+II and cyclothymia, 1 year prospective	SUD			No effect	No effect	No effect	No effect	No effect	No effect	No effect

Abbreviations: U. = university, SUD = substance use disorder, AUD = alcohol use disorder, OR = odds ratio, RR = risk ratio, HR = hazard ratio.

When no specification on type of BD, in/outpatient status etc. is listed, no information was presented in the paper. Substance use disorder is "lifetime" when no information on whether it is current or lifetime is listed. The studies are presented chronologically, except when all or parts of participants are shared between studies. In this case, the studies are grouped together. Effect sizes (OR, RR and HR) are listed with 95% CI in parentheses if these are reported in the study

Excessive cannabis use is associated with earlier age at onset in bipolar disorder

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Abstract

Objective: To investigate which factors are associated with age at onset in bipolar disorder with a specific focus on excessive alcohol and cannabis use, and the sequence of the onsets of excessive substance use and bipolar disorder.

Methods: We investigated a naturalistic sample of 151 patients with bipolar I and II disorder receiving psychiatric treatment. Whether the presence of excessive substance use prior to bipolar disorder onset or the type of substance used (alcohol or cannabis) was associated with differences in age at onset was investigated using hierarchical, multiple linear regression analyses, adjusting for potential confounders.

Results: Patients with excessive alcohol use had a significantly later onset compared to patients with excessive cannabis use. Excessive general substance use prior to bipolar disorder onset was associated with a later onset. However, excessive cannabis use was associated with an earlier onset whether it preceded or followed bipolar disorder onset, also after adjusting for possible confounders. Excessive use of alcohol or other substances was not independently associated with age at onset in multivariate analyses.

Conclusions: Alcohol use was associated with a later onset compared to cannabis use, suggesting different relationships to the onset of bipolar disorder. Lifetime use of cannabis predicted an earlier onset, independent of the sequence of onsets. This indicates that an early onset may increase the risk of cannabis use and that cannabis use may trigger bipolar disorder in vulnerable individuals.

Key words: Bipolar disorder, age at onset, cannabis

Introduction

The age at onset (AAO) of bipolar disorder (BD) varies from adolescence to mid-adulthood¹, but the reasons for the variation are not fully known. Recent studies find differences in AAO between research sites, with early AAO more often reported from US studies than from European studies²⁻⁴ even though there are exceptions^{3;5;6}. These variations have been attributed to factors ranging from differences in genetic loading to recruitment biases or methodological discrepancies^{2;6;7} such as the definition of illness onset.

However, several other factors have been shown to affect AAO in BD. A family history of affective disorder has been associated with an early onset⁸⁻¹⁰. Most studies find a similar AAO for men and women¹¹, while some report earlier onsets in females^{12;13}, and others earlier onsets in men with BD I³. The subtypes of BD (BD I and II) appear to have a similar AAO¹⁴; however, earlier onsets in either BD I or II was also recently reported^{3;7}. In addition, experiences of childhood trauma was associated with an earlier onset^{15;16}.

The relationship between substance abuse and AAO in BD is poorly understood. The risk for substance abuse (especially of illicit substances) appears to be increased for patients with childhood- and adolescent onset compared to adult onset^{13;17-21}, and it has been hypothesized that AAO and substance abuse may share a common genetic etiology¹³. These studies, however, did not differentiate between the types of substances used. Alcohol and cannabis are the two most frequently used substances in BD²²⁻²⁵. To the best of our knowledge the association between type of substance of abuse (alcohol or cannabis) and AAO has not been investigated in previous studies.

Substance abuse may both be a cause and a consequence of early BD onset. One line of research has investigated whether differences in AAO depend on the sequence of the onsets of BD and substance abuse. A later onset has been found among patients with substance abuse that precedes the BD²⁶⁻³². There is also evidence for a less severe clinical course^{28;33-35} and lower rates of family history of affective illness²⁷ in BD secondary to substance abuse. This has lead to the hypothesis that substance abuse could be necessary for a manifestation of BD in these individuals^{27;28;33}. Most studies have focused on either alcohol abuse or substance abuse in general, and the potential to precipitate BD has been proposed for both alcohol^{33;36}, cannabis²⁹ and even for any substance of abuse³⁵.

The pharmacological effects of various substances of abuse are often different, and alcohol and cannabis appear to have different effects on the course of an established BD. In a prospective study, cannabis use coincided with

or preceded hypomanic or manic symptoms, while alcohol use coincided with or preceded depressive symptoms³⁷. Recently, there has been focus on the relationship between BD and cannabis use in prospective epidemiologic studies. These indicate that cannabis use in the general population is associated with development of manic symptoms³⁸, and that lifetime cannabis use is associated with a fivefold increase in the risk of developing BD³⁹.

Only one study has investigated the sequence of the onsets of BD and cannabis use disorders and its relationship to AAO. This indicated that patients with a primary cannabis use disorder had a later onset compared to patients with no cannabis use disorder or a secondary cannabis use disorder²⁹. This has not been replicated, and there is a need for further studies that simultaneously evaluate the associations between AAO and excessive alcohol or cannabis use. It is here of particular interest whether or not the excessive substance use was present before the BD onset.

In the present study we investigated a sample of 151 BD patients. We had the following research questions:

- 1) Does AAO differ between patients with excessive alcohol use, excessive cannabis use and patients using neither of these substances?
- 2) Do type of excessive substance use (i.e. alcohol or cannabis) and the presence of excessive substance use prior to the BD onset independently predict AAO after adjusting for possible confounders?

Methods and materials

Participants

A hundred and fifty-one patients with DSM-IV diagnosed bipolar disorder (BD I n=91 and BD II n=60) participated in the study. This patient sample is part of an ongoing study of schizophrenia and BD (the Thematically Organized Psychosis (TOP) study). Patients were recruited consecutively from the psychiatric units (in- and outpatient) of the three major hospitals in Oslo from 2003 to 2008. Participants were excluded if they had a history of moderate/severe head injury, neurological disorder, developmental delays, age outside of 18–65 years, or if they did not speak a Scandinavian language. All participants gave informed consent, and the project was approved by the Regional Committee for Medical Research Ethics as well as the Norwegian Data

Inspectorate. Data on the relationship between AAO, illness severity and time to first treatment for parts of this sample are reported elsewhere ⁷.

Clinical assessment

Clinical assessments were carried out by trained clinical psychologists and psychiatrists. Diagnoses were established using the Structured Clinical Interview for DSM-IV (SCID), modules A-E (American Psychiatric Association, 1994). All interviewers were trained based on the training program at UCLA CA, USA and participated in regular diagnostic consensus meetings. A good inter-rater reliability was achieved with an overall kappa score of 0.77 (95% CI: 0.60-0.94). AAO was defined as the age when the first SCID-verified affective episode (depressive, hypomanic, manic or mixed) began. Sociodemographic and clinical variables were cross-checked with participants' medical charts and with information from interviews with close family members if relevant. A family history of depression, BD, schizophrenia, and other psychotic disorders among first degree relatives (i.e. mother, father, brothers and sisters) was obtained through patient interviews. Patients having a minimum of one first-degree relative with one or more psychiatric disorders were considered to have a family history. A family history of other psychotic disorders than BD was considered since several recent studies have shown common heritability for BD and schizophrenia ^{40;41}. A family history was collected for 148 of the patients. Of these, 62 (42%) had a positive family history of any lifetime affective or psychotic disorder; 41 (27%) of depression, 20 (14%) of BD and 6 (4%) of psychotic disorder. Four patients had a family history of both BD and depression, and one patient had a family history of both BD and psychosis.

Substance use assessments

Each patient reported lifetime substance use (daily, weekly, monthly, or occasional/no use) for all substances for the following life periods: 11-15 years, 16-20 years, 21-27 years, 28-44 years, 45-60 years, and 60+ years. Patients that either 1) met criteria for a DSM-IV substance use disorder (SUD) or 2) had predominantly *daily* use of alcohol and/or predominantly *weekly* use of a non-alcoholic substance through at least one of the life periods above (i.e. for a minimum of four years) were considered excessive substance users and included as such in the subsequent analyses. In an earlier study, we have shown that the use patterns and correlates of excessive substance use are similar for patients with SUD and patients with excessive substance use according to definition above ⁴².

Age at onset of excessive substance use was deemed to be either 1) the age when DSM-IV abuse/dependence criteria were first met, or 2) the age when the patient started daily use of alcohol or weekly use of (a) non-alcoholic substance(s). Twenty-eight patients (19%) had excessive use of alcohol, 24 patients (16%) had excessive use of cannabis, and 11 patients used both. Patients who used both were similar to the patients who used cannabis only and not to the patients who used alcohol only for all relevant clinical and sociodemographic characteristics, and were therefore grouped together with the cannabis-only patients in the bivariate analyses for research question 1. But to further ensure that the differences between the alcohol and cannabis groups were not due to the characteristics of the patients using both alcohol and cannabis, follow-up analyses were conducted where these patients were excluded. Among the 88 patients with neither excessive alcohol nor cannabis use, three patients (3%) had excessive use of other substances. These 88 patients are subsequently referred to as non-users.

Sequencing of onsets of BD and excessive substance use

For research question 2, the total sample was subdivided into two groups based on the presence (secondary BD) or absence (primary BD) of excessive substance use prior to the first affective episode. This dichotomous variable is subsequently referred to as the *sequencing* of onsets. The small group of patients (n=6) whose onsets of the first affective episode and excessive substance use occurred within the same year were categorized as secondary BD. This was done because excessive substance use to a greater degree than BD has a gradual rather than an abrupt onset. Since all patients in this study eventually were diagnosed with BD, affective episodes associated with substance use in patients with no previous BD episode were used as markers for AAO. Using these criteria, 117 (77%) patients had primary BD and 34 (23%) had secondary BD. Patients with primary BD could theoretically develop excessive substance use after the onset of BD, and data showed that 32 patients (21%) subsequently did. Sociodemographic and clinical characteristics in the two groups are described in table 1.

PLEASE INSERT TABLE 1 HERE.

Statistical Analysis

All analyses were done using the Statistical Package for the Social Sciences (SPSS) version 16.0. Statistical significance was determined using the .05 level and 2-tailed tests of significance. One-way ANOVAs with

Tukey's post-hoc tests were used to compare the groups on continuous variables. Dichotomous variables were analyzed with Chi-square tests with corresponding post-hoc analyses performed using Chi-squares with a Bonferroni corrected alpha-level for the three group comparisons set to 0.017. Pearson correlations were used to assess bivariate associations between the dependent and independent variables. A two-way ANOVA was used to investigate the possible interaction effects of type of substance use and sequencing. The contributions of the independent variables were then further explored with multiple regression analyses. Possible confounders of the relationships between AAO and type of substance or sequencing were chosen on the basis of differences found in bivariate analyses and findings from earlier studies. They were identified as gender, type of BD (I versus II), a family history of affective/psychotic disorders, and excessive use of other substances than alcohol or cannabis. Possible mediators that did not show significant or trend level effects were not entered in the final model. In the present material, age was highly correlated with AAO due to the focus on including mainly non-chronic patients in the study. Since preferred substance (alcohol or cannabis) may be a cohort phenomenon and influence AAO, age was still entered into the model. This model provided a better mathematical fit despite the colinearity. The variance accounted for by some of the other variables was, however, reduced. The analysis was performed hierarchically with several steps: first, gender and age; second, BD type and family history of affective/psychotic disorders; third, sequencing; and fourth, excessive alcohol and cannabis use. Reported are increase in R^2 at each step, beta-values, and their corresponding statistics from the final model.

Results

Patients with excessive alcohol use had a significantly later onset compared to patients with excessive cannabis use, and showed a trend in the same direction relative to the non-users (Table 2). Excessive alcohol users and non-users were older than the cannabis users. The excessive alcohol users also had a significantly later onset of the excessive substance use than the cannabis users. The proportion of patients with a family history of affective or psychotic disorders was significantly higher among the cannabis users compared to the alcohol users. There was a trend towards a greater proportion of females among the non-users compared to the alcohol users ($p=0.065$). Follow-up analyses excluding patients using both alcohol and cannabis did not give any changes regarding group wise differences for age, AAO and age at onset of excessive substance use, or for the proportion with BD I or a family history of affective/psychotic disorder. The difference in the proportion with excessive use

of other substances was, however, no longer significant (18% vs. 25%, $\chi^2=0.40$, $p=0.53$) implying that excessive polysubstance use was a characteristic of the excluded group.

PLEASE INSERT TABLE 2 HERE.

AAO was earlier for primary BD compared to secondary BD (21.8 ± 9.0 vs. 25.9 ± 9.8 , $p=0.02$) (Table 1) and for cannabis users compared to alcohol users (19.5 ± 5.4 vs. 27.9 ± 11.8 , $p=0.005$) (Table 2) in both primary and secondary BD as illustrated by Figure 1. There were no interaction effects between sequencing and type of substance use.

PLEASE INSERT FIGURE 1 HERE

The bivariate analyses revealed significant correlations between AAO and gender, age, BD type, excessive cannabis use, and sequencing (Table 3).

PLEASE INSERT TABLE 3 HERE

The multiple regression analysis showed that sequencing and excessive cannabis use significantly predicted AAO after adjusting for gender, age, and BD type. Age and BD type also made significant contributions to the model, while gender contributed on a trend level (Table 4). Excessive use of alcohol was not a significant predictor, nor was family history or excessive use of other substances. Lower age, BD II, primary BD and excessive cannabis use independently predicted an earlier onset, with gender and age explaining 29% of the variance, type of BD 3%, sequencing 5% and alcohol and cannabis use another 5%, with a total of 41% of the variance explained. Without age entered in the analysis, gender explained 5% of the variance, type of BD 3%, sequencing 2.5% and alcohol and cannabis use another 13.5%, with a total of 24% of the variance explained. Since sequencing was entered before cannabis use in the analyses, cannabis use appeared to predict an earlier onset regardless of whether it preceded or followed the onset of the BD.

PLEASE INSERT TABLE 4 HERE.

Discussion

The main finding of the present study was that excessive cannabis use predicted an earlier onset, while secondary BD predicted a later onset, after adjusting for possible confounders. Furthermore, excessive alcohol users had a later onset compared to excessive cannabis users.

We found clear differences between the alcohol users and the cannabis users. In addition to a later onset, the alcohol users were older, had a later onset of the excessive use, a lower prevalence of family history and lower rates of use of other substances compared to the cannabis users. This has, to our knowledge, not been shown before. Our findings also suggest differences in sequencing between the alcohol and the cannabis users; for the alcohol users, the mean AAO was earlier than the mean age at onset of the excessive substance use, while for the cannabis users the mean AAO was later than the mean age at onset of the excessive substance use. There was, however, no interaction effect between type of substance use and sequencing on AAO.

The later onset in alcohol users compared to cannabis users may indicate that different mechanisms are involved in the relationships between the development of BD and these two most frequently used substances. Although the present study is cross-sectional and does not allow conclusions of causality, taken together, our findings may indicate that cannabis to a greater extent than alcohol influences the onset of BD. This is in line with two recent studies on acutely ill patients with a broad spectrum of psychotic disorders, showing that cannabis abuse/dependence was associated with an earlier onset of the psychotic disorders after adjusting for abuse/dependence of other substances including alcohol ^{43;44}. Our findings indicate that the association between AAO and excessive cannabis use is present also in a pure BD sample. This is in line with the growing evidence that cannabis use is a risk factor for developing manic symptoms and BD ^{38;39}, while alcohol abuse seems to increase the risk for depressive rather than manic symptomatology ^{37;45}. Furthermore, in a recent study on prodromes of first manic psychotic episode, 68% of patients were found to have substance use disorders in the prodromal phase, of which 82% used cannabis ⁴⁶. Also, it is fairly well established that cannabis use composes a risk factor for the development of psychosis/schizophrenia ⁴⁷. The fact that schizophrenia and BD have many clinical features in common as well as overlapping pathophysiology ⁴⁸ increases the plausibility that cannabis use may act as a risk factor also in BD.

The association between cannabis use and early onset in the current study was present also after adjusting for sequencing, and appears to exist also when the excessive use develops after the BD. This indicates that an early onset increases the risk of subsequently developing excessive cannabis use. This is in accordance with earlier findings of an association between early BD onset and drug abuse ^{19;49}, which may have several explanations. Some authors have proposed that patients with early onset may share a common increased genetic vulnerability mediating both BD and excessive drug use ¹³. Family history did not independently predict AAO in the present study. However, the family history rates of affective/psychotic disorders among the cannabis users were high.

Having a close family member with a severe psychiatric disorder in addition to experiencing affective episodes early in life may also represent a substantial psychosocial burden, leaving the patient at increased risk for illicit substance use.

The present finding that cannabis use predicts an earlier onset regardless of sequencing is in contrast to earlier findings of a later onset of BD secondary to cannabis ²⁹. This discrepancy could be due to differences in methodology and sample characteristics. One explanation may be the high family history rates in our sample of excessive cannabis users, on which no data were presented in the previous study. Higher family history rates may indicate high vulnerability for BD, which may interact with excessive cannabis use to cause an early onset in these patients. The complex relationship between AAO, type of substance used, sequencing and family history should be further explored in a greater sample allowing comparisons on several subgroup levels.

One possible explanation for the association between early onset of BD and excessive cannabis use could be a cohort effect, i.e. that people born in the last decades may be at greater risk for developing excessive cannabis use than patients born earlier due to trends in substance use or increased availability. However, since excessive cannabis use still predicted AAO after adjusting for age, this cannot explain the finding. The association between earlier onsets and cannabis use was also present after adjusting for family history and excessive use of other substances. Thus, it is unlikely the present findings can be explained in terms of these potential confounders.

The present finding that secondary BD predicted a later onset (relative to primary BD) is highly consistent with earlier studies ²⁶⁻³². We also demonstrate that this effect remains significant even after adjusting for several variables known to be associated with AAO (gender, BD type, family history, type of substance used), further supporting the hypothesis that the excessive substance use may trigger BD. We do not replicate earlier findings that family history is associated with AAO ⁸, or that family history rates are lower in secondary BD compared to primary BD ²⁷. We do, however, demonstrate that the family history rates are higher among the cannabis users compared to the alcohol users and the non-users. Patients' reports of family history of psychiatric disorders is a somewhat crude measure ⁵⁰, which may explain these inconsistencies. Furthermore, the full range of vulnerability markers and risk factors for BD are not yet known, thus other factors may have confounded the results.

In the multivariate analyses we found that BD II disorder independently predicted an earlier onset, with the same trend for female gender. Recent studies on the association between AAO, gender and BD type are somewhat

diverging; one study reported earlier onsets in females but no differences regarding BD type ¹², while another reported that males and BD I had an earlier onset compared to females and BD II ³. The latter finding is in contrast to the present study, while the former showed similar results. This suggests that gender and BD type are relevant when investigating AAO, but future studies are needed to clarify these questions. Also, the findings of the present study suggest that the prevalence of excessive cannabis use could account for differences between populations in AAO.

The present study has some limitations. Data on substance use and illness characteristics including AAO were gathered retrospectively, risking recall bias. There is, however, no reason to believe that this should affect the subgroups differently. Furthermore, some of the subgroups in the bivariate analyses are small, increasing the risk of type II errors.

Conclusion

Excessive cannabis use is associated with an early onset regardless of whether it precedes or follows the BD, while excessive use of alcohol or other substances are not independently associated with AAO. General excessive substance use prior to BD onset is associated with a later onset. The relationship between cannabis use and BD onset should be further investigated in prospective studies.

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Table 1. *Sociodemographic and clinical characteristics in primary BD and secondary BD*

	Primary BD	Secondary BD	Statistics
	N=117	N=34	
Age, y, mean (SD)	36.50 (12.2)	33.7 (10.4)	t=1.2, df=149, <i>p</i> =0.227 ^a
AAO, y, mean (SD)	21.8 (9.0)	25.9 (9.8)	t=-2.3, df=149, <i>p</i>=0.020^a
Age at onset of excessive substance use, y, mean (SD)*	27.0 (11.6)	20.1 (7.0)	t=2.9, df=64, <i>p</i>=0.005^a
Gender, female, n (%)	74 (63.2)	18 (52.9)	$\chi^2=1.2$, df= 1, <i>p</i> =0.278 ^b
Type I BD, (%)	68 (58.1)	23 (67.6)	$\chi^2=1.0$, df=1, <i>p</i> =0.318 ^b
Family history of affective/psychotic disorder, n (%)	45 (39)	17 (52)	$\chi^2=1.6$, df=1, <i>p</i> =0.204 ^b

BD=Bipolar Disorder. AAO=Age at onset of BD. Y=Years. *For the 32 patients with excessive substance use in the primary BD group.

^aStudent's t-test, ^bChi-square test.

Significant *p*-values are typed in bold.

Table 2. Sociodemographic and clinical characteristics of patients with excessive alcohol use, excessive cannabis use or use of neither

	No use, n=88 (A)	Alcohol use, n=28 (B)	Cannabis use, n=35 (C)	Statistics
Age, y, mean (SD)	36.6 (12.0)	42.0 (11.9)	29.2 (7.5)	F=10.9, df=2,150, p<0.001 , A, B>C (trend A<B)
AAO, y, mean (SD)	22.6 (9.2)	27.0 (11.8)	19.5 (5.4)	F=5.5, df=2,150, p=0.005 , B>C (trend A<B)
Age at onset of excessive substance use, y, mean (SD)	21.0 (6.1)*	30.9 (11.3)	17.0 (2.7)	t=6.0, df=61, p<0.001
Gender, females, n (%)	60 (68)	13 (46)	19 (54)	$\chi^2=5.1$, df=2, $p=0.079$ (trend A>B)
Bipolar disorder, type I, n (%)	54 (61)	15 (54)	22 (63)	$\chi^2=0.7$, df=2, $p=0.717$
Family history, n (%)	32 (38)	8 (29)	22 (63)	$\chi^2=9.0$, df=2, p=0.011 , A, B<C
Excessive use of other substances, n (%)	3 (3)	5 (18)	13 (37)	$\chi^2=2.8$, df=1, $p=0.092^a$

AAO=age at onset of bipolar disorder. y=years. No use: no excessive substance use. Alcohol use: excessive use of alcohol.

Cannabis use: excessive use of cannabis. Family history includes affective or psychotic disorders.

*3 patients with excessive use of other substances

^aOnly B and C were included in analysis.

Table 3. *The correlations between AAO and socio- demographic and clinical variables*

Variable	AAO
Age	0.52**
Gender	-0.22**
BD type (I versus II)	-0.19*
Family history of affective/psychotic disorder	-0.15
Age at onset of excessive substance use	0.54**
Excessive cannabis use	-0.19*
Excessive alcohol use	0.13
Excessive use of other substances	-0.14
Sequencing	0.19*

AAO=Age at onset. Data are expressed as Pearson correlations

*p<0.05

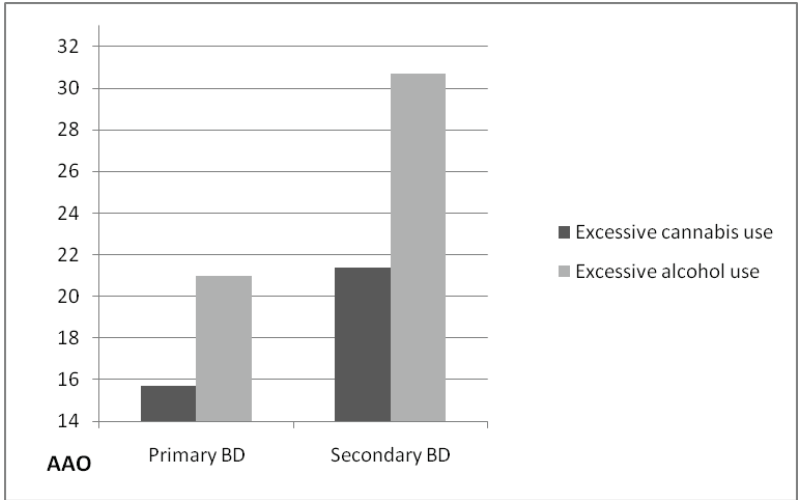
**p<0.01

Table 4. *Multiple regression analysis of the effect of independent variables on age at onset*

Block No., Variable	R ² Change	Beta (SE)	95% Confidence Interval for B	t	P value
Constant		17.33	(10.30 to 24.36)	4.87	<0.001
1					
Female	0.29	-2.42 (1.27)	(-5.43 to -0.17)	-1.91	0.058
Age		0.36 (0.06)	(0.25 to 0.46)	6.48	<0.001
2					
BD I	0.03	-2.73 (1.23)	(-5.16 to -0.30)	-2.22	0.028
3					
Secondary BD	0.05	8.20 (1.79)	(4.67 to 11.72)	4.59	<0.001
4					
Excessive cannabis use	0.05	-6.01 (1.8)	(-9.59 to -2.43)	-3.32	0.001
Excessive alcohol use		-0.33 (1.43)	(-3.16 to 2.50)	-0.23	0.817

Final model, R²=0.41, F=16.65, p<0.001

Figure 1. Relationship between AAO, sequencing and type of substance use



AAO=Age at onset, years. BD=bipolar disorder.

